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American Journal of Diseases of Children

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REPORT ON A CASE OF MALIGNANT THYMOMA WITH NECROPSY *

NATHAN CHANDLER FOOT, M.D.
BOSTON

One does not often encounter malignant tumors of the mediastinum and it is seldom that they are to be procured in as fresh a state of preservation as that which I shall report:

REPORT OF CASE

CASE.—The patient, G. S., aged 9 years, was sent in to the service of Dr. James S. Stone, in the Children's Hospital, from a suburban hospital April 30, 1919, with the diagnosis of mediastinal tumor.

Previous History.—He was a normally delivered, full-term child, with a negative family history. Ever since his fourth year he had had frequent attacks of tonsillitis, which led to the removal of his tonsils and adenoids when he was 6 years old. During the winter months he had frequent colds and coughing which usually lasted two to three weeks at a time; these would occur as often as every month.

Present Illness.—His present illness began with a gradual onset of coryza and inspiratory dyspnea, one month prior to admission. He could not lie flat in bed, having well marked orthopnea. Two weeks after onset, his mother noticed swollen veins at the base of his neck, just above the clavicle. She stated that roentgen-ray examination at the local hospital was negative. The patient was better at the time of his admission to the Children's Hospital, able to lie flat and sleep on one pillow; he had occasional fits of gagging and coughing, which would awaken him at night, but was otherwise pretty comfortable. He did not raise much, if any, mucus when he coughed, there was no cyanosis, no convulsions, no bleeding from the nose or the mouth. He had no pain in his chest, no night sweats or night cries.

Physical Examination.—There was dullness on both sides of the sternum from the first to the fifth rib, breath sounds and voice sounds were increased; there was bronchovesicular breathing. Breath sounds were more nearly normal on the left than on the right side. There was a dorsal scoliosis of the spine to the right. The patient was round-shouldered. The heart sounds were clear and normal; precordial dullness measured 2.5 by 8.5 cm. The aortic second sound was louder than the pulmonic second. The abdomen was negative. The extremities were of equal size with veins showing prominently in places. Blood pressure, left: 130 mm.; right: 120 mm.

Roentgen-Ray Examination.—This showed (Fig. 1) a large mediastinal tumor, occupying the upper central portion of the chest; stereoscopic roentgenograms showed that it was anterior to the great vessels. The veins in the anterior and lower part of the neck were prominent, and there was slight enlargement of the veins of the upper part of the chest anteriorly.

* From the pathological laboratory of the Children's Hospital, Boston, Mass., and the Department of Pathology, Harvard Medical School, Boston, Mass.

E.m.

Laboratory Findings.—The urine was normal. Leukocytes, 12,000; erythrocytes, 4,460,000. Differential count: Polymorphonuclears, 69 per cent.; mononuclears, 31 per cent. The blood smear showed nothing abnormal. Hemoglobin, 90 per cent. The von Pirquet test was negative. Except for two rises in temperature to 99 on the days he was roentgenographed, the temperature curve was comparatively flat.

Diagnosis.—A tentative diagnosis of mediastinal abscess or enlarged mediastinal nodes was made on admission.

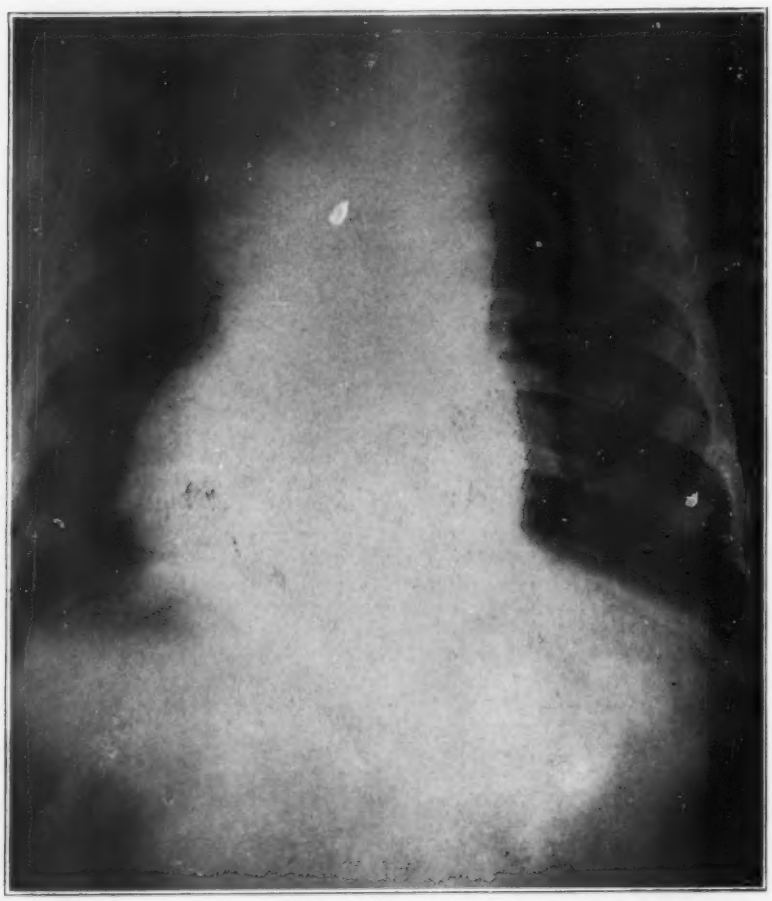

Fig. 1.—Roentgenogram of tumor, taken during life by Dr. Percy Brown.

Operation.—The patient was taken to the operating room one week after admission, for the purpose of making an exploration. He took his ether well, holding the cone himself, until partially anesthetized. As the anesthesia became complete he grew markedly cyanotic and the ether was immediately stopped, the usual restoratives, including oxygen being used. The boy's color improved steadily and became almost normal. His heart seemed to be in good condition. He never regained consciousness, however, and one-half hour after starting anesthesia he suddenly became very pale, and his heart and respiration stopped abruptly. Tracheotomy was not performed, as there was no hope of relieving the obstruction by this means. A necropsy was performed four hours later.

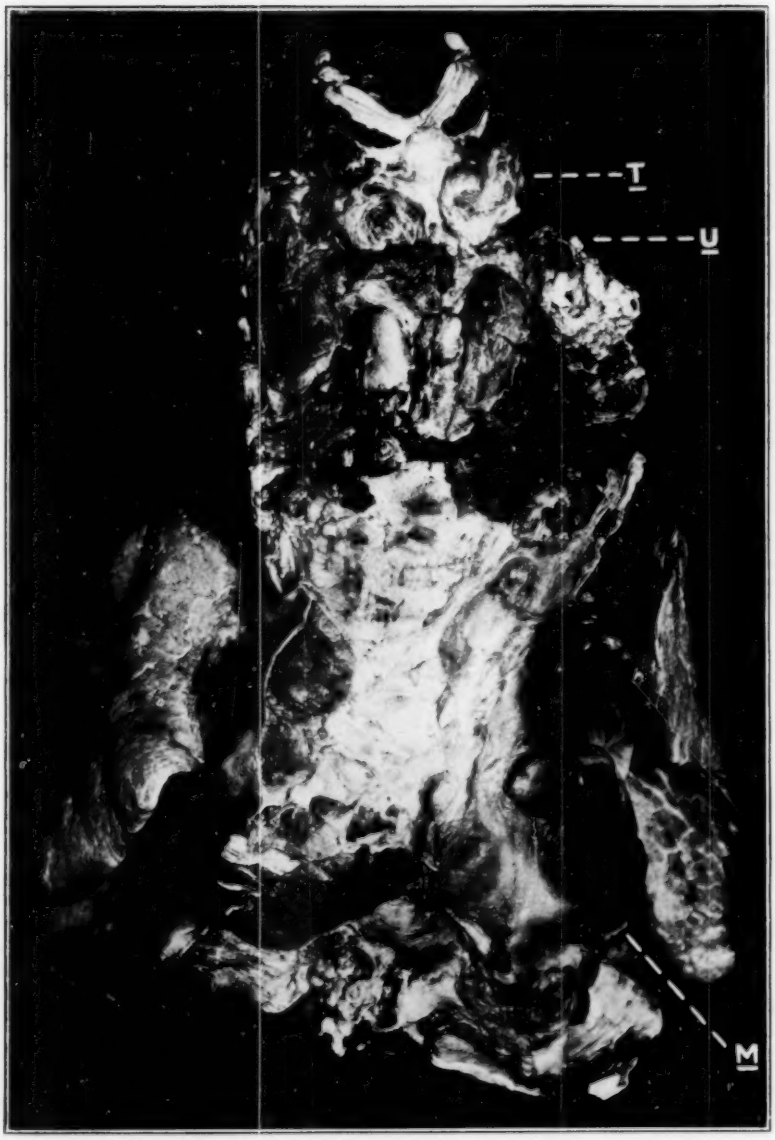

Fig. 2.—The tumor viewed from in front. T = thyroid gland; U = upper limit of tumor; M = metastases into pericardium, which is unopened. Lungs on either side.

Necropsy Report.—The body is that of a well nourished, well developed, white male child, 139 cm. in length. There is no rigor mortis, except in the lower jaw; postmortem lividity is present in dependant portions. There is nothing remarkable about the head. A bulging mass is palpable above the suprasternal notch, extending as high as the thyroid and firm and lobulated. The left side of the thorax is noticeably arched and protruding; otherwise not externally abnormal. Primary incision, extending from suprasternal notch to mons pubis. The abdominal contents are in situ, but there are adhesions between the gallbladder and pylorus and the transverse colon and liver. The intestines as a whole, are congested. There is a small accessory spleen, 1.2 cm. in diameter, situated just off the lower pole of the spleen proper and about 1.5 cm. distant therefrom. The liver projects 1.5 cm. below the free margin of the ribs. The mesenteric lymphnodes are all enlarged, some of them to 2 cm. in diameter. They show coarse, whitish follicles through their capsules and the largest of them is almost completely caseous. The diaphragm is at the first rib on the right, at the fifth interspace on the left. On opening the thorax one notes that the costal cartilages cut easily and that the muscles covering the thorax are of good color. On removing the sternum, a tumor of very extensive growth is encountered.

This tumor lies in the anterior mediastinum, is adherent to, but does not infiltrate the sternum and extends from the thyroid gland above to the diaphragm below. The organs of the neck and thorax were removed in toto, in order that they might be studied more intelligently. The pericardium contains 200 c.c. of clear, straw colored fluid; its inner surface is studded with small, granular tumor masses; its outer aspect shows several large infiltrating masses of tumor tissue, about 2 cm. in diameter and 0.75 cm. in thickness, as shown in Figure 2. The heart is firmly contracted and shows small masses of a similar nature on its epicardium, varying from 1 mm. to 1.3 cm. in diameter and penetrating the myocardium to a slight extent.[1] The lungs show no internal abnormalities on section, although there are metastatic foci in the pleura. For the sake of coherence, the tumor will be described later, its gross and microscopic peculiarities being combined.

Abdomen: The spleen is very firm, purplish red and weighs 101 gm. On section, it drips bloods, its pulp is firm and does not strip readily on the knife blade. The splenic corpuscles are coarse and prominent, whitish in color; the trabeculae are normal in size and number. The organ contains one small metastatic nodule, spherical in shape and cartilaginoid in consistence. It is yellowish white and measures 0.5 cm. in diameter.

Liver: Weight, 830 gm. It is dark reddish brown in color, mottled with a definite nutmeg pattern. Its capsule is everywhere smooth and glistening, except where there are adhesions with neighboring viscera. At the apex of its convex surface, near the middle of the falciform ligament and to the right of it, is a spherical mass, yellowish white and 1.2 cm. in diameter. It is very firm in consistence. On the under surface of the left lobe is another such mass, stellate in outline and 1.5 cm. in diameter, which is completely calcified. The cut surface of the liver drips blood, is finely patterned in a nutmeg design of reddish brown and seems not unduly fibrous or greasy. The gallbladder contains viscous, olive green bile which is readily expressed through the papilla of Vater.

Stomach: This organ is of normal size, its mucosa velvety and of the usual appearance; there is marked congestion and a large hemorrhagic erosion in the duodenum, just below the pylorus. It is 2.5 cm. in diameter; the mucosa is ulcerated and there is evidence of fresh hemorrhage here. Some bloody mucus lies in the lumen of the gut. The intestines show similar areas of hemorrhage here and there and they are congested, as a whole, the congestion being apparently passive in type. Pancreas: This is of normal size and consistence. Kidneys: They weigh together 218 gm. Their capsules strip readily, exposing

1. Grawitz: Deutsch. med. Wchnschr. **37**:2357, 1911.

a smooth surface, with injected stellate venules. The organs show congestion on cutting them open, are of a dark red color, drip blood and the congestion is apparently of a passive type, similar to that in the other organs. The ratio of medullary to cortical diameter is normal, there is nothing abnormal about the pelves, ureters, nor urinary bladder.

Fig. 3.—The tumor viewed from behind, the lungs on either side.

Restrictions by the parents prevented examination of the cerebrum.

Microscopic Examination.—The spleen shows congestion of its pulp, with increase in the pulp cells; the malpighian corpuscles are well formed; the trabeculae are normal. There are many eosinophil leukocytes in the sinuses, both of the myelocytic and polymorphonuclear type. The liver shows passive con-

gestion, with slight fatty infiltration, not in excess of physiologic limits. The metastatic (?) nodules are either completely necrotic or calcified and give little or no clue as to their original composition. The large caseous mesenteric lymph node shows typical tuberculosis, with a zone of miliary tubercles surrounding a caseous center.

Examination of Tumor.—Macroscopic: The tumor in the mediastinum is roughly conical in shape, its base measures 8 cm. laterally and 11 cm. anteroposteriorly, while its axis is 11 cm. in height. It is homogeneous, for the greater part, pearly yellowish white and occupies the entire mediastinum, surrounding all the large vessels, the bronchi, trachea and the peribronchial lymph nodes. It is lobulated, the lobules being of a type to suggest local overgrowth of a single organ, rather than aggregations of enlarged nodes. Cross sections made at various levels (clearly seen in the posterior view in the illustration, Fig. 3) show that it has included everything as high as the thyroid gland; it is as though moulten wax had been poured into the anterior mediastinum and had flowed out laterally and posteriorly before hardening; in the thorax the

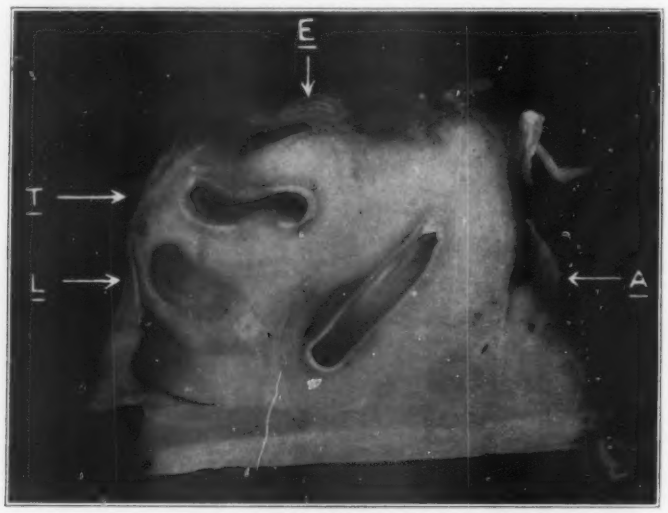

Fig. 4.—Transverse section of tumor at level of arch of the aorta. E = esophagus; T = trachea; L = an included lymphnode. An arrow, "A," points to the diagonally situated arch of the aorta.

esophagus alone has escaped inclusion. The tumor resembles cornstarch blanc mange in its yellowish white color, but is of an extremely dense and almost cartilaginous consistence. The trachea is compressed anteroposteriorly, until it is a mere slit, a millimeter or so in this diameter (Fig. 4). This compression is present practically throughout its entire length. Here and there lymph nodes are embedded in the tumor mass, but they are totally different in appearance, being of a soft consistence and more yellow tinge. The tumor shows areas of necrosis at intervals throughout its substance, but they are few and widely separated from one another. They are of irregular outline, somewhat softer in consistence than the tumor and of a canary yellow color. The growth has metastasized by way of the lymphatics into the pleura and pericardium in its immediate vicinity, where it forms several plaques as already described. It will readily be seen that the tumor, then, occupies the site of the thymus and has encroached directly on the pericardium, heart, pleura and lungs.

Microscopic: The tumor is made up of innumerable lymphocytoid cells which, at first glance, might be taken for microlymphocytes. Closer examination, in sections stained with Mallory's eosin-methylene blue, shows that they differ from these in several respects: They are somewhat larger, more polygonal in outline, have an acidophile rather than a basophile cytoplasm and their nuclei are vesicular, contain a nucleolus and are poor in chromatin when compared with those of the microlymphocytes (Fig. 5). They lie, furthermore, in a dense feltwork of collagen fibrils and fibers, which in some cases form basket-

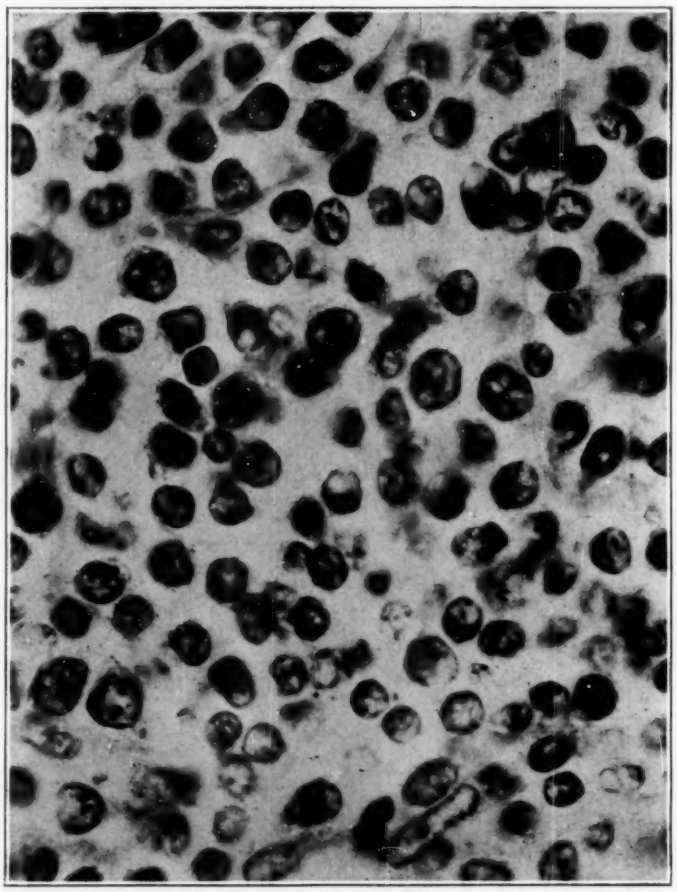

Fig. 5.—Oil-immersion photomicrograph of nonfibrous portion of the tumor. Slightly more than 1,000 diameters magnification. Phosphotungstic acid-hematoxylin.

like nests, or alveolar spaces in which the tumor cells lie more or less crowded together (Fig. 6). Often, too, one can demonstrate delicate anastomosing filaments, or processes from the cytoplasm of these cells, which connect them either with one another, or with the fibrous reticulum in their neighborhood. They do not give the oxydase reaction, when stained by Goodpasture's [2] method. Their

2. Goodpasture, E. W.: J. Lab. & Clin Med. **4**:442, 1919.

size is fairly constant in certain localities (Fig. 5), some parts of the tumor showing larger cells than do others, but the cells of each part are usually of about the same size. They average from 4.5 to 6.0 microns, occasionally attaining a long diameter of 7.5 microns. Mitoses are very thickly distributed and usually occur in the smaller type of cells. There are a good many eosinophil leukocytes present, both types being scattered throughout the tumor and usually being more or less locally grouped. Some rather larger cells are found containing one or two large masses of eosinophil material, probably phagocytosed erythrocytes. Besides the tumor cells, there is a larger type of cell of a vesicular character; with large, pale nucleus (from 10 to 14 microns) and a well marked nucleolus. Their cytoplasm may be vacuolated; when it is thinned out and

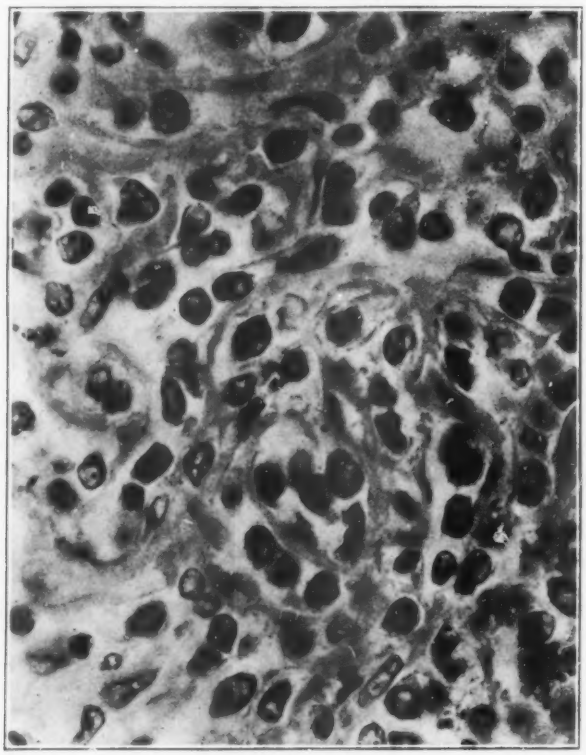

Fig. 6.—Showing the fibrous reticulum of the tumor; oil-immersion photomicrograph, 1,000 diameters. Phosphotungstic acid-hematoxylin.

stained with phophotungstic acid hematoxylin one finds blue fibrils in its substance. These cells closely resemble swollen fibroblasts, though they may represent thymic reticulum cells. They are often piled up locally in the vicinity of blood vessels, where they might be mistaken for young Hassal's corpuscles. As vessels can usually be demonstrated as being intimately connected with their appearance, it seems more likely that they are endothelial phagocytes, or fibroblasts. There are a few giant cells at the margin of the necrotic areas in one of the ten or more blocks cut from the tumor; they are somewhat like those seen in a Hodgkin's granuloma, with large, vesicular nuclei which are

more or less lobulated. Sometimes they are multinuclear, but they never have as dense a cytoplasm as the so-called "foreign body giant cells." They are found only in the situation mentioned.

The stroma, or reticular network of collagen fibrils, stains bright red with acid fuchsin and deep red with phosphotungstic acid hematoxylin. It varies much in density, being in the form of a delicate reticular network here and a dense fibrous matrix in another situation. The two types are shown in Figures 5 and 6. It is this feltwork that gives the tumor its deceptively cartilaginoid consistence.

Lymph nodes taken from near the tumor show hyperplasia, many eosinophils and a considerable number of small cells which are indistinguishable from the tumor cells and lie among typical lymphocytes, with which they contrast rather sharply. There are no giant cells in these nodes, and their reticulum appears to be normal and not fibrosed. There are one or two nodes, however, which show a very remarkable hyperplasia and proliferation of their endothelial elements, particularly those of the lymph sinuses between nodules. These are often massed into thick bands or cords, the vascular endothelium in this situation seemingly sharing in the process, although to a lesser degree. In those places where the tumor has penetrated the myocardium, this is a direct infiltration from the epicardial fatty tissue near the anterior interventricular sulcus and near the apex, to a depth of 270 microns. The structure of the growth does not differ microscopically here from that seen elsewhere.

SUMMARY OF FINDINGS

We have a very hard, lobulated mediastinal tumor, occupying chiefly the anterior mediastinum; lying just behind the sternum, but not infiltrating the bone. It shows metastasis by direct lymphatic extension, with three possible minor metastases at a distance. It does not penetrate the lung nor other neighboring organs much more deeply than their serous coverings or sacs. It is composed chiefly of small cells, resembling microlymphocytes, but having vesicular nuclei, acidophil cytoplasm and tending very slightly to anastomose with one another by means of slender processes. This applies only to a decided minority of their number, the majority being unconnected with each other, or discrete. The rest of the tumor is chiefly collaginous connective tissue. Neighboring lymph nodes, while they show a few discrete tumor cells in their sinuses, are usually respected by the tumor and not incorporated in its mass.

REVIEW OF LITERATURE

The literature on this subject is characterized by its comparative scantiness and by the wide divergence of opinion shown by the various writers as to the true status of these tumors. Such textbooks as Borst's,[3] Lewin's,[4] Ribbert's [5] and Wollf's [6] pay but passing attention to them. Schridde,[7] in Aschoff's "Pathologische Anatomie," gives a good description of tumors of thymic origin, which is fairly comprehensive considering its brevity. Since 1911, very little has been written

3. Borst, M.: Die Lehre von den Geschwülsten, Wiesbaden, 1902.
4. Lewin, C.: Die bösartigen Geschwülste, Leipzig, 1909.
5. Ribbert, H.: Geschwulstlehre f. Aertze u. Studierende, Bonn, 1904.
6. Wollf, J.: Lehre von der Krebskrankheit, Jena, 1911.
7. Schridde, H.: Aschoff's "Pathologische Anatomie," Jena, 1911, 177; Münch. med. Wchnschr. **58**:2593, 1911.

on the subject. Of the more recent articles, one by Ewing,[8] and another by Vanzetti,[9] present extremely good reviews of the various theories that have been advanced as to the origin and character of thymic tumors, and the authors report several cases and give full bibliographies on the topic. Rubaschow's[10] case report and article is very helpful, while Wiesel's[11] much longer paper on the pathology of the thymus, which stresses the clinical features of these tumors, is valuable but rather rambling and prolix. Rubaschow has compiled a list of the tumors of the thymus described up to 1911, combining one of Hoffmann's which brought them up to 1896. It totals about seventy-five cases, of which fifty-two were described as "sarcomata" of various sorts, twelve as carcinomas and the rest variously. He gives the names of the writers concerned and the dates of publication. Since 1911 one can find but few reports, less than a dozen.[12]

Rubaschow reports a case more closely corresponding to the one described in this paper than any that could be found, although it occurred in a man, aged 62. The "type cells" were very small lymphocytoid affairs, and there were aggregations of larger cells, such as I have already described. Two of Ewing's cases come very close to ours in appearance. It is possible, in reviewing the literature, to find descriptions of tumors in which the type cells vary all the way from small, disconnected lymphocytoid cells, through larger, more or less anastomosing cells, to a definitely epithelial type of large cell, which may finally attain a degree of differentiation resembling that of the epidermoid carcinoma, on the one hand, and an adenoma or adenocarcinoma, on the other. Our case stands at the lowest point in the scale; Rubaschow's and Chiari's[13] may be slightly more advanced. Two of Ewing's come next, with larger, more polygonal cells, which have a tendency to anastomose, or to be connected with the reticulum by delicate processes (just as was found in the upper portions of our tumor). Vanzetti's[9] is still further differentiated, the cells in his tumor being frankly epithelial in appearance; and then come numerous examples of true carcinoma.

The presence of much connective tissue and many eosinophils have led several authors to compare this tumor with Hodgkin's granuloma, and to suspect an infectious origin. Those of us who consider the

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8. Ewing, J.: Surg., Gynec. & Obst. **22**:401, 1916.
9. Vanzetti, F.: Arch, per le sc. med., Torino **40**:264, 1916.
10. Rubaschow, S.: Virchow's Arch. f. path. Anat. **206**:141, 1911.
11. Wiesel, J.: Ergebn. d. allg. Path. u. path Anat. **15**:416, 1912
12. Barbano, C.: Pensiero Med. **2**:701, 1912. Roccavilla, A.: Gazz. d. osp. **34**:903, 1913; Riforma med. **21**:337, 1915. Simmonds, M.: Ztschr. f. Krebsforsch. **12**:280, 1912. Speed, K.: Surg. Clin. **1**:643, 1917. Perrero, E.: Riv. di. clin. pediat. **9**:241, 1913.
13. Chiari, O. M.: Zentralbl. f. Path. **22**:8, 1911.

latter disease a form of neoplasm can dismiss this contention by attributing the presence of increased connective tissue and the eosinophils to a sympathetic overgrowth or irritation of elements already present in the parent organ. Giant cells, of whatever type found, obviously present no stumbling block.

HISTOLOGY OF THYMUS

Before going any further into this discussion, it would be well to consider the general aspects of the thymus in its relation to tumors of the mediastinum. It will be seen that so long as there is uncertainty as to the histology of this organ, just so long will there be doubt and disputes as to the histogenesis of tumors arising therefrom. Of the various histologic elements of the organ, three are the subject of speculation and dispute. The small thymic cell of the cortex ranks first as a bone of contention; is it a lymphocyte, or is it a modified form of epithelial cell? Dantchakoff,[14] Hammar [15] and Maximow take the former view; while Bell, Prenant, Schridde, and more recently Pappenheimer [16] claim its descent from the epithelium.[17] A clearer understanding of the difficulties surrounding this question will be gained by reading Hammar's "Fuenfzig Jahre Thymusforschung," [15] or Pappenheimer's splendid exposition.[16]

The occurrence of eosinophil cells in the thymus is another cause for discussion. Are they eosinophil leukocytes derived from the circulating blood, or are they cells peculiar to this organ? Hassal's corpuscles, although admittedly epithelial in character, represent another unknown quantity, insofar as their physiologic function is concerned.

THYMUS ORIGIN OF TUMOR

When we come to consider tumors derived from these elements, we naturally enough encounter the same questions, the same dissensions, the same difficulties. Are they epithelial and hence carcinomas, or should they be called sarcomas and lymphosarcomas? Not only do we have to deal with such problems, but the question arises as to which mediastinal tumors may be considered thymic in origin and which derived from the lymph nodes of this region.

It seems to be more or less agreed that the following facts point to the thymic origin of a tumor:

1. The situation of a large, not too lobulated, firm tumor at the site of the thymus, in the anterior mediastinum.

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14. Dantchakoff, V.: J. Exper. Med. **24**:87, 1916.
15. Hammar, J. A.: Anat. Hefte **19**:1-274, 1909; 43, 201, 1911.
16. Pappenheimer, A.: J. Med. Res. **17**:1, 1910.
17. From a personal conversation with Dr. Pappenheimer, a few weeks ago, I surmise that he has changed his opinion and joined the "lymphocytic camp."

2. Extension downward behind the sternum, without infiltrating the bone.

3. Involvement of the pericardium and pleura by direct lymphatic extension.

4. A resemblance to thymic tissue on histological examination. The finding of Hassal's corpuscles is helpful, but not essential.

Ewing, Schridde, Rubaschow and Letulle [18] are fairly well in accord on these points, some being more specific in their statements than others. Virchow (quoted by Wiesel [11]) maintained that the thymic tumors involved the pericardium first, while the lymphosarcomas attack the lungs or pleura. Hoffman (quoted by Vanzetti [9] and Wiesel [11]) denied that one could make any decision in the matter, the two types of tumor being absolutely indistinguishable one from the other. He appears to be alone in his opinion, nobody seeming to accept so sweeping a view. He also denies that the presence of Hassal's corpuscles proves anything at all. Letulle [18] states that the parenchyma of the lung can only be invaded secondarily by thymic tumors, thus paraphrasing Virchow's statement. He imposes other conditions, such as eccentric pressure on neighboring viscera, but they seem less essential. Vanzetti feels that the small-celled type of thymic tumor so closely resembles a true lymphosarcoma, that one must be extremely careful in diagnosing one from the other; a fact that no one will dispute.

Another point on which most authorities agree is that the tumors are apt to be of the small-celled or sarcomatoid type in youth; while they are large-celled epithelial, or sarcomatous, in later years, after fifty. In this connection it is interesting to note that Rubaschow's case occurred in a man, aged 62, and yet was of a definitely small-celled type, which he considered epithelial.

When one compares the thymoma with a true lymphosarcoma, one finds many similarities; but this is, perhaps, to be expected in view of the similarity of the small thymic cell and the lymphocyte. The following points seem to be against the lymphocytoid type of thymoma being a true lymphosarcoma.

1. The type cell is almost identical with the small thymic cell.
   (a) The nucleus is large, more or less ovoid and may contain a well marked nucleolus.
   (b) The cytoplasm is often acidophil, never strongly basophil like that of the microlymphocyte, and may be present in sufficient quantities to give the cell a polygonal outline. Anastomosing processes may be present.

18. Letulle: Arch. Gen. de med. **2**:641, 1890.

2. Lymphnodes taken from near the tumor, although they may show isolated tumor cells in their sinuuses under the microscope, are not definitely incorporated in the tumor mass. They stand out clearly demarcated, even when surrounded on all sides by the tumor, both when viewed in the gross, or with the microscope. Rubaschow has stressed this point. They seem to hold themselves aloof from the tumor process, not only locally, but also in more distant parts of the body. Metastases, when they occur at a distance from the tumor, generally do so in the spleen or liver instead of in lymphnodes, as one would expect, were this a true lymphosarcoma. The mesenteric nodes in our cases are enlarged, but show either tuberculosis or simple hyperplasia, no tumor metastases being found.

3. Lymphoblasts and collections thereof are not found in the tumor to any appreciable extent, mitoses occurring in the smaller cells, or in larger cells totally dissimilar from the large lymphocyte.

4. There is a variable tendency to form alveoli, or nests of small cells, although lumina are not definite enough to warrant speaking of glandular structure.

SUMMARY

The information to be gleaned from a review of this subject, as well as from what little I can add to it, seems to point rather strongly to an epithelial origin of the tumor in question. One starts with a cell which is almost, but not quite identical in appearance with the microlymphocyte, but once it begins to differentiate the similarity is rapidly lost. It would seem to be wisest not to put too much stress on an argument based on a series of transitional stages pieced together from groups of cases occurring in individuals of different ages and reported by an equally variable number of observers with opposed points-of-view. Such a series is, nevertheless, very suggestive and not unsupported by supplementary evidence from the embryologic standpoint. On the one hand, as Ewing has said, are the small-celled, sarcomatoid tumors; on the other the carcinomatous; while between these are all the intergradations, which to him suggest an infectious process when they appear in the same tumor. There is very little reason to regard such a tumor as ours as being of infectious origin, while there is a great deal to point towards its being a true neoplasm. Although the presence of eosinophils and a few large cells are reminiscent of Hodgkin's granuloma, these could be explained by the irritation of the neoplasm on its host, so that it seems best not to consider the two conditions as being at all related to each other.

CONCLUSION

In conclusion, there seems to be little doubt that these small-celled thymic tumors fulfill the conditions we have already reviewed and are, whether lymphosarcomas or not, still of thymic origin and different from the lymphosarcomas that originate in lymphnodes. The decision of their true status rests with the histologist, who must first determine without a doubt, the origin of the small thymic cell. Once this has been done, the question will be settled automatically, so far as the pathologist is concerned.

I am much indebted to Prof. Lewis Bremer, of the Department of Anatomy of the Harvard Medical School, for the use of his photomicrographic apparatus, and to his staff for their aid and advice as to its use. Dr. Percy Brown has kindly supplied me with the Roentgenograph which is reproduced in this article.

PRECIPITINS FOR EGG ALBUMIN IN STOOLS*

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CHICAGO

The preparation of the stools was the same in these cases as that reported in a previous article.[1]

Anti-egg white rabbit serum of a titer of 40,000 was used. Titer equals highest dilution of egg white in salt solution in which the serum produced precipitate by contact method after one hour at room temperature.

The first group (Table 1) consisting of 103 stools from 24 cases showed three positive reactions. These stools were all from children two years or over. Two of the positive reactions occurred in the case of idiocy (Case 6). This child had a large quantity of egg in the diet since it was about the only food which she would take readily. To the other children egg was usually given in the form of ice cream and pudding only on Sunday afternoons, but occasionally during the week. The single other positive reaction that occurred in the stool of Case 4 occurred within forty-eight hours after taking this diet; but of seventeen other stools with the same relation to the diet, no positives were found.

After this initial group, it was decided to study a few cases with egg albumin given to the amount of a teaspoonful each day. For this three different types of cases were chosen. Case 1, a control case, was fed through a gastrostomy wound; the second case, a case of intestinal infantalism, and a third one of general eczema. In seventeen stools obtained from these children only one showed a doubtful reaction (Table 2).

In the third group of thirty-three cases of infants 2 years old or under, there were 221 stools. In only two of these cases was the age over 1 year. Many of them were newborn infants who had received a dilute albumin water to the amount of 10 c.c. of egg albumin to 500 c.c. of water, which was given to these infants in place of the usual boiled water. From this group 221 stools were examined with five positive reactions. One of these reactions occurred in a new-born infant who had been given the egg albuumin mentioned above. In the other three children who gave positive reactions, we know of no way to account for these, since in no instance was egg albumin present in the diet.

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* From the McCormick Memorial Institute and Children's Ward of the Presbyterian Hospital.

* Read before American Pediatric Society, May 30-June 1, 1920.

1. Hektoen, L., and Grulee, C. G.: Am. J. Dis. Child. **18**:1 (July) 1919.

TABLE 1.—Examination of Stools of Older Children for Egg Albumin

No.	Diagnosis	Age, Years	No. of Stools	Positive Reaction
1	Chorea; myocarditis; Ludwig's angina; tonsillitis	8	28	0
2	Epilepsy	10	9	0
3	Syndactylism	5	2	0
4	Appendicitis	8	9	1
5	Chronic osteomyelitis (fibula)	9	9	0
6	Idiocy	3	14	2
7	Fractured arm	6½	2	0
8	Otitis media; mastoiditis	4	2	0
9	Osteomyelitis os calcis	8	5	0
10	Abscess of cervical glands	6	2	0
11	Diabetes mellitus	2½	1	0
12	Chorea	8	5	0
13	Skull fracture	4	1	0
14	Congenital glaucoma	2½	1	0
15	Chronic ileocolitis	2	2	0
16	Eye injury	5	2	0
17	Chorea	8	2	0
18	Otitis media	2	1	0
19	Cholecystitis	12	1	0
20	Tenoplasty for old poliomyelitis	10	1	0
21	Tuberculous meningitis	3	1	0
22	Rectal polyp	4	1	0
23	Encephalitis lethargica	2½	1	0
24	Chronic tonsillitis	7½	1	0
	Total	..	103	3

TABLE 2.—Test Cases Given One Teaspoonful of Egg Albumin per Day

No.	Diagnosis	Age, Months	No. of Stools	Positive Reaction
1	Stricture of esophagus	13	2	0
2	Intestinal infantalism	22	6	0
3	Eczema	19	9	1 (?)
	Total	..	17	1 (?)

TABLE 3.—Results of Examination of Stools of Infants

No.	Diagnosis	Age	No. of Stools	Positive Reaction
1	Prematurity	Newborn	10	0
2	Prematurity	Newborn	4	0
3	Prematurity	Newborn	1	0
4	Normal	Newborn	3	0
5	Intracranial hemorrhage	Newborn	1	0
6	Normal	Newborn	6	0
7	Normal	Newborn	3	1
8	Normal	Newborn	5	0
9	Normal	Newborn	3	0
10	Normal	Newborn	4	0
11	Normal	Newborn	2	0
12	Normal	Newborn	2	0
13	Normal	Newborn	4	0
14	Normal	Newborn	2	0
15	Normal	Newborn	1	0
16	Normal	Newborn	2	0
17	Hydrocephalus meningocele; prematurity	1 mo.	16	0
18	Prematurity	5 wks.	9	0
19	Hare lip; cleft palate	2 mos.	10	0
20	Pylorospasm	2 mos.	7	0
21	Infantile eczema	11 wks.	16	0
22	Infantile eczema	3 mos.	14	2
23	Pylorospasm	3 mos.	7	0
24	Decomposition	3 mos.	1	0
25	Pylorospasm	14 wks.	20	0
26	Rumination	5 mos.	14	1
27	Congenital syphilitic hydrocephalus	6 mos.	8	0
28	Hydrocephalus	6 mos.	9	1
29	Weight disturbance	7½ mos.	23	0
30	Rickets	1 year	5	0
31	Meningeal hemorrhage	1 year	5	0
32	Infantile eczema	21 mos.	2	0
33	Cervical cellulitis; pyelocystitis	2 years	2	0
	Total	.....	221	5

It would seem from these results that egg albumin is in nearly every instance completely broken down by the digestive processes in infants and children. This holds good not only for children and older infants, but also where the egg albumin is used in small quantities for the new-born as well. There is only one other possibility, and that is that the egg albumin instead of being broken down in the process of digestion is absorbed unchanged. We do not feel that specificity of the precipitin reaction for egg albumin is to any degree disproven by the fact that it was found to be positive in stools where no egg had been present in the diet. We would be inclined to attribute such reaction to the complexity of the stool.

I wish to take this opportunity to thank Dr. Ludvig Hektoen, who has been kind enough to have the precipitins prepared and the experiments done under his personal supervision; and to Dr. B. E. Bonar for the preparation of the fecal extracts.

THE HEMORRHAGIC TENDENCY AS A FREQUENT CAUSE OF CRANIAL HEMORRHAGE OF THE NEW-BORN *

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At the meeting of the Section on Diseases of Children of the American Medical Association in Chicago, June, 1918, I expressed the belief that an important factor in intracranial hemorrhage occurring during, or soon after birth, was the so-called hemorrhagic tendency of the new-born, frequently expressed in hemorrhages from the mucous surfaces in various portions of the body.[1] A case in point was cited of an infant, 3 days old, in which, following diagnosis, a cranial decompression was performed, revealing a general hemorrhagic oozing of the pia. Convulsions and other cranial pressure symptoms were relieved, but vomiting of blood, and hemorrhage from the rectum, caused death a day later, in spite of prompt blood transfusion from the father. The free use of lumbar puncture and of human blood serum, horse serum or thromboplastin was suggested at that time in every instance where intracranial hemorrhage of the new-born is suspected. I said in part:

> . . . I am firmly convinced that all of the causes are not maternal. Probably many cases occur after rapid delivery in which the cause lies not with the mother but with the child. I am sure many of us have seen hemorrhage of the new-born in connection with intracranial hemorrhage in infants. I think we would see many more if the children lived long enough. I think many of the cases which do not show rupture in the meningeal artery are not frank hemorrhages so much as oozing of the vessels of the pia, perhaps not producing the classical symptoms so early as hemorrhage from the meningeal artery. For that reason we can say that there is a hemorrhagic tendency, some degrees of permeability of the vessels, not going on to the extent that will produce characteristic vomiting of blood, but increased fragility of the vessels of the infant, which does produce, even after rapid labor, symptoms of hemorrhage of the brain. There is no doubt that great relief can be obtained by lowering intracranial pressure through lumbar puncture. As has been stated by the essayist, it is of great value as a diagnostic measure, and should never be omitted in any case of intracranial hemorrhage in an infant. It certainly can do no harm to use some method to increase the coagulability of the blood—blood serum, citrated blood or something of that sort, in attempting to offset the tendency to hemorrhage that undoubtedly exists in many of these children.

At the Providence Hospital, Washington, D. C., within the last fifteen months, this procedure has been followed in seven cases. In all new-born infants showing within twelve to twenty-four hours after

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* From the Pediatric Department of Georgetown University and the Obstetrical Wards of Providence Hospital.

1. Brady, Jules: Discussion by Foote, J. A. M. A. **71**:347 (Aug. 3) 1918.

birth respiratory distress and blueness, with or without muscular rigidity and twitching, lumbar puncture was performed. In every instance where these symptoms were observed within twenty-four hours after birth, the lumbar puncture showed amounts of blood, varying from a deep to a light claret color, and occasionally small clots. Both horse serum and thromboplastin were used hypodermically. Ten c.c. was the amount injected, the horse serum being employed, however, in five of the seven cases. One of these infants died; the others recovered uneventfully. In only one was lumbar puncture repeated. Six of these which we have been able to trace seem normal in every way so far, although the ultimate results cannot be predicted definitely at this early date.

Corroborative of these clinical observations is the report by Dr. Margaret Warwick of thirty-six necropsies at the University of Minnesota, on still-born infants or those dying within a short period after birth.[2] Fifty per cent. of these showed hemorrhages in the dura, over the brain surface or in the ventricles. Only one of these was a forceps case. Two out of eighteen were born dead. In eight, or 50 per cent., of those showing cranial hemorrhage, hemorrhages were found in other organs. Five of these infants vomited blood before death, and all showed increased coagulation time. Warwick mentions the frequency of punctate hemorrhages seen in the pleura and peritoneum in routine necropsies of the new-born. A number of reports of hemorrhage in the fetus or in various organs of the new-born infant are on record. Paul[3] found retinal hemorrhage of the infant in 50 per cent. of premature labors, 40 per cent. of prolonged labors, and 20 per cent. of normal labors.

Osler once reported finding a cranial hemorrhage in the brain of a fetus, the mother of which had died from typhoid fever. Kundrat[4] believes that many cranial hemorrhages in the new-born occur without any visible symptoms, the small amount of exuded blood absorbing rapidly. Moreover, cases are frequently mistaken for atelectasis, and this same writer found that practically all cases show partial atelectasis of one or both lungs. This is well borne out by the clinical symptoms of blueness and difficult breathing, which frequently dominate the clinical picture.

It is interesting, in view of these observations, to report still another infant with cranial hemorrhage and frank hemorrhages from the mucous surfaces which responded to early treatment in a surprising manner.

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2. Warwick, Margaret: Am. J. M. Sc. **158**:295, 1919.
3. Paul: Inaug. Dissert., Halle, 1910.
4. Cited by Warwick, loc. cit.

REPORT OF CASE

CASE (8076).—Baby, delivered after a long labor, midforceps operation by Dr. Davenport White. Breathed normally and cried. No traumatic marks on head. Weight, 8 pounds 4 ounces. Twelve hours after birth became blue, and respiration was labored. Some tonic twitching of left arm and hand. A monotonous cry. Coagulation time of blood exceeded nine minutes. Was given 10 c.c. horse serum. Lumbar puncture was made, 10 c.c. of fluid was withdrawn, red in color with numerous small soft clots. Red blood cells abundant microscopically. Fifteen hours after delivery infant vomited red blood mixed with mucus. Hemorrhages occurred within a few hours from the rectum, nose, stomach and ear. Ten c.c. of thromboplastin was given under the skin on the appearance of blood in the vomitus. No further hemorrhages occurred, the infant began to suck vigorously, and except for a febrile course for a few days, had no further symptoms. At the age of 9 weeks infant shows an average gain of 2 ounces a week on artificial food, but tolerates increased feeding rather poorly.

The surgical treatment of this condition is one which yields brilliant results when pressure symptoms allow a focal diagnosis. The work of Cushing [5] and of Sharpe [6] emphasizes that simple surgical relief of pressure often suffices to avert the horrible after paralysis known as Little's disease, and that this treatment has its distinct indications. Sharpe's splendid essay is rich in valuable information concerning the surgical aspects of this condition, and the indications which in certain circumstances make a resort to surgery an inevitable proceeding. However, early recognition of the condition and treatment directed toward increasing blood coagulability will be beneficial in that large number of cases where the hemorrhage comes from very small vessels, even as a preliminary toward surgical decompression, when that is found necessary.

It is true that hemorrhage may occur in the infant's skull, produce all the classical symptoms and yet be followed by apparent recovery without any special treatment directed toward blood coagulability or the relief of pressure. Two such cases have come under my personal observation. One of the patients is now 6 years old, the other 4 years. Neither of these children shows any muscular abnormality today. This is corroborative of Kundrat's [4] observation, and of the necropsy work of Wehe [7] who found that 12 per cent. of 959 infants at necropsy showed evidence of having had cranial hemorrhage. It also speaks for an unusual capacity of the infant organism in absorbing coagulated blood, which may be taken advantage of in treatment along the lines I have suggested.[8]

5. Cushing, Harvey: Am. J. M. Sc. **130**:563, 1905.
6. Sharpe, W.: Internat. Clin. **4**:258, Series 29.
7. Wehe, A.: Inaug. Dissert., Kiel, 1889.
8. Seitz: Zentralbl. f. Gynäk. **36**:1, 1912.

CONCLUSIONS

1. The tendency toward hemorrhage in the new-born is frequently first manifested as intracranial hemorrhage, and it is important to recognize that this may be and often is a local manifestation of a general condition.

2. The early use of lumbar puncture and the hypodermic administration of substances that tend to increase blood coagulability are rationally indicated in every case of suspected intracranial hemorrhage of the new-born, even prior to operation.

3. The suggestion that blood coagulation tests be performed as a routine on the new-born infant is one that merits consideration.

ACTIVE IMMUNIZATION AGAINST DIPHTHERIA IN A LARGE CHILD-CARING INSTITUTION

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NEW YORK

During the past few years our ability to detect antitoxin immunity in diphtheria has been greatly simplified by the introduction of the Schick test. Since this test has been shown to be a very accurate measure of the body's antitoxic immunity, we are now able by its use to measure the value of any new form of prophylactic treatment which depends on the production of antitoxin. A new form of preventive treatment is the toxin-antitoxin injection first advocated by Theobald Smith and William H. Park, and first actually employed in human beings by von Behring. During the past five years we have been able to use this active immunization and to control it by means of the Schick test in the Home for Hebrew Infants. This institution is especially adapted for this work, as the same children can be observed and retested for a period of about five years; furthermore, the ages of the children coincide with the most frequent age incidence of diphtheria.

During the year 1915, diphtheria had been endemic in the institution, and there were six deaths due to the disease. It was a problem, therefore, to attempt to reduce if possible the morbidity and consequent mortality. We welcomed the opportunity to separate, by means of the Schick tests, those immune from those susceptible, and to attempt to increase the number of the former by means of toxin-antitoxin injections. The diphtheria toxin used in the Schick test was obtained in bulk from the Research Laboratory of the New York City Department of Health. Dilutions for the test were made from the pure diphtheria toxin as follows: One hundred times the minimum lethal dose for the guinea-pig was diluted up to 10 c.c. with physiologic sodium chlorid solution. This primary dilution does not deteriorate appreciably for a period of two weeks if kept cold in the icebox. The final dilution, good for twenty-four hours only, is made by taking 1 c.c. of the primary dilution, and adding 99 c.c. of physiologic sodium chlorid solution. The amount injected intracutaneously for the Schick test is 0.2 c.c. of the final dilution representing $\frac{1}{50}$ minimum lethal dose for the guinea-pig. The injection is best made on the anterior surface of the forearm in its upper third, using a 1 c.c. Record syringe, with a fine platinum iridium needle. Schick injects $\frac{1}{50}$ minimum lethal dose for the guinea-pig in only 0.1 c.c. of physiologic sodium chlorid solution. The use of 0.2 c.c. of the final dilution is preferable because the

area of the reaction is greater in extent and the chance of error in the amount injected is less. In borderline cases the Schick method gives the stronger reaction.

A negative Schick test denotes that there is sufficient antitoxin in the tissues to neutralize the diphtheria toxin injected, and, therefore, enough to protect the individual. A strongly positive Schick test denotes that there is no antitoxin in the tissues and, therefore, the individual is not protected by antitoxin. Bactericidal substances may, however, be present. Therefore, the person is probably, but not certainly, susceptible. A moderately positive reaction indicates a faint trace of antitoxin. The positive reaction appears usually in from twelve to twenty-four hours, but may be delayed another twenty-four or forty-eight hours. It is characterized by a circumscribed area of redness and slight infiltration at the site of the injection, measuring from 1 to 2 cm. in diameter. This persists usually for at least seven or ten days and then fades with superficial scaling and a dark brown pigmentation. I have seen the pigmentation persist for as long as three or four months. The positive reaction is dependent on the local destructive action of diphtheria toxin on the tissue cells in the absence of antitoxin. The moderately and faintly positive reactions which occur in those having faint traces of antitoxin are characterized by lesser degrees of redness and infiltration than the strongly positive. The pseudoreaction, a pure sensitization phenomenon occurring in older children and adults, was rarely seen in the young children tested.

For convenience, the strongly positive reaction can be designated as +, the moderately and slightly positive as $\pm$ and the very faintly positive as $\underline{\pm}$. Children giving $\pm$ and $\underline{\pm}$ reactions have been included in the tables with the positive cases. In this institution, for the sake of greater safety they were in all cases given actively immunizing toxin antitoxin injections.

The tables summarize the reactions obtained in children of various age groups from 1 month to 6 years. For comparison I have appended tables showing Shick's and Zingher's results.

As shown in Table 1, 37 per cent. of the children in all probability were susceptible to diphtheria. These susceptible children were most frequently encountered between the ages of 6 months and 4 years. They were fewest in number in infants younger than 6 months or older than 4 years. The infrequency of positive reactions during the first half year of life is owing probably to an immunity inherited from the mother. That this immunity may gradually be lost by the infant was well illustrated by retesting the infants from time to time. It was found that a number of those who gave negative reactions during the first two years of life became positive later on; in other words, their

inherited passive antitoxic immunity was gradually lost. Of a total of 119 children under 1 year of age giving negative tests, nineteen, or 16 per cent., became positive from three to six months later. When first tested, ten of these were in their first half year of life, and nine were in the second half year. Thirteen of 108 negative children, or 12 per cent., became positive during the second year, and five of 125 negatives, or 4 per cent., became positive during the third year of life. Table 4 illustrates this loss of inherited immunity.

The tests in certain families made on members under 3 years of age are also of interest. Of seventy-two families tested, two or more members gave the same Schick test in fifty-five families. Variations occurred in seventeen families as follows: In thirteen instances the younger member gave the positive Schick test and the older the negative; in four instances the younger member (in each case under 1 year of age), gave the negative Schick test, while the older gave the positive. This last variation is undoubtedly due to the disappearance of a passively transmitted immunity. These variations in the negative Schick tests during the first years of life emphasize the importance of frequently retesting infants in institutions. The retests should be done at least every three months.

It is worthy of note that when diphtheria was epidemic at the institution in 1915, in not a single instance did a child with a negative Schick test contract the disease. This record was uninterrupted until January and February, 1920, when influenza was epidemic. At that time nonspecific croup, in contradistinction to diphtheritic croup, was a rather frequent complication of influenza. Diphtheria antitoxin was administered to the croupy children having a positive Schick test and all recovered, except one. This child died, possibly of a complicating laryngeal diphtheria since the throat culture was positive for diphtheria bacilli. A necropsy was not made. Diphtheria antitoxin was administered in two very severe cases of croup and bronchopneumonia with negative Schick tests. One of these patients was intubated and died of bronchopneumonia. Diphtheria bacilli were not obtained from the cultures. The other patient had ulcerative stomatitis with extension of membrane to the pharynx and larynx and bronchopneumonia. A bronchoscopy was done for diagnostic purposes, and intubation was necessary shortly thereafter. Death followed in a few hours. Repeated throat cultures had been negative for diphtheria bacilli, cultures taken directly from the larynx and from a bit of tracheal exudate were positive. The facts that the child had given a negative Schick test and that a large dose of antitoxin had no effect, lead us to believe that the bacilli found in the trachea were not inciting the disease.

TABLE 1.—Results from Immunization Against Diphtheria at Home for Hebrew Infants

Age	Total	Negative Schick	Positive Schick	Percentage of Positive Schick Tests
1 to 6 months	97	76	21	21.6
6 months to 1 year	115	43	72	62.6
1 to 2 years	221	108	113	51.1
2 to 4 years	409	258	151	36.9
4 to 6 years	234	185	49	20.9
Total	1,076	670	406	37.7

TABLE 2.—Zingher's Results at Immunization

Age	Total	Negative Schick	Positive Schick	Percentage of Positive Schick Tests
1 to 6 months	101	82	19	18.8
6 months to 1 year	84	40	44	52.3
1 to 2 years	52	28	24	46.1
2 to 4 years	127	82	45	35.4
4 to 6 years	108	88	20	18.5
6 to 8 years	25	22	3	12.0
Total	497	342	155	31.1

TABLE 3.—Schick's Results at Immunization

Age	Total	Negative Schick	Positive Schick	Percentage of Positive Schick Tests
New-born	291	275	16	5.0
First year	42	24	18	43.0
2 to 5 years	150	55	95	63.0
5 to 15 years	264	133	131	50.0
Total	747	487	260	34.8

TABLE 4.—Results of Retesting Negative Schick Cases

Age	Negative Tested	Change to Positive Within Six Months	Percentage of Cases Changing to Positive
1 month to 1 year	119	19	16.0
1 to 2 years	108	13	12.0
2 to 3 years	125	5	4.0

TABLE 5.—Schick Retests on 252 Positive Children After Immunizing with Diphtheria Toxin-Antitoxin Mixtures

Time Interval after Injection	Number Tested	Results		Per Cent. Negative
		Positive	Negative	
Group 1. 3 to 4 months	252	68	184	73
Group 2. 9 to 10 months	130	12	118	91
Group 3. 22 months	50	0	50	100

Having ascertained that 37 per cent. of the inmates of our institution were susceptible to diphtheria, we proceeded to attempt to immunize these 252 children as follows: In the slightly or moderately positive, and the strongly positive cases three injections were made; in the faintly positive, two injections were made. The injections were given subcutaneously at intervals of one week, in the outer arm at the insertion of the deltoid muscle. Children under one year received 0.5 c.c., and those over 1 year 1 c.c. of the diphtheria toxin-antitoxin mixture at each injection. There was occasionally a little redness and swelling at the site of the injection and a rise in temperature in twenty-four hours up to 102 F., coming down to normal in another twenty-four hours. Vomiting occurred in one case and collapse in another with immediate recovery of the patient.

In order to test results, the children who had received the above treatment were subjected to the Schick test at two month intervals. Of these children, 252 in number, all of whom had been positive to varying degrees before injection, a large proportion were found to have become subsequently negative. The immunity developed in the children at different intervals; so that the later tests show a larger percent immune.

Of the 252 children originally tested, only 130 remained in the institution at the end of 9 or 10 months, and of this number only fifty remained at the end of twenty-two months.

From Table 5 it will be seen that very striking results were obtained. In from three to four months after toxin-antitoxin injections, 77 per cent. of the positive cases had become negative. In the group of fifty cases which were followed up as late as twenty-two months after injection, 100 per cent. had become immune. These marked results show the great practical importance of the active immunization of individuals susceptible to diphtheria, whether they are inmates of institutions or at large in the community. In this way an institution can be rendered practically immune. These results also emphasize the possible permanence of the immunity conferred, lasting perhaps during the life of the individual.

It is interesting to note that during a period of two years there was not a single case of diphtheria at the Home for Hebrew Infants. During this same period there were only about six positive diphtheria cultures in all throat and nose conditions. That this is mere coincidence is possible, but one may draw the conclusion that the toxin-antitoxin injections were probably instrumental in freeing the institution of diphtheria, despite the fact that for a time there were present a small number of susceptible children not immunized. It is also

possible that the toxin-antitoxin injections rendered the nose and throat an unfavorable site for the growth of diphtheria bacilli. The blood being antitoxic the local toxin produced by the presence of the bacilli would not irritate the epithelial cells and thus the oral and nasal mucuous membrane would be rendered unfavorable for the growth of diphtheria bacilli.

CONCLUSIONS

1. Schick tests made on 1,076 children in an institution during a period of five years show that a negative Schick test is evidence of the presence of sufficient antitoxin in the tissues to protect the individual against diphtheria infection.

2. The moderate or slightly positive tests denote an insufficient amount of antitoxin in the tissues to protect the individual. The tests called very faintly positive show possibly sufficient antitoxin to protect; however, it is possible that the transfer of virulent organisms to these individuals may cause them not only to become carriers but to suffer from a superficial infection without any constitutional toxemia.

3. Tests made on seventy-two families showed that the younger members of the same family usually gave corresponding reactions to the Schick test. Where variations did occur, the younger member gave usually the positive and the older the negative reaction. Infants under 6 months, because of the transmitted immunity of the mother, were exceptions to this rule.

4. Changes in the Schick reaction from negative to positive during the first three years of life, due to the loss of an inherited immunity, were found to be sufficiently numerous to justify retesting during this period at intervals of a few months. This procedure is especially desirable in infant asylums.

5. The full duration of the active immunity conferred on individuals susceptible to diphtheria by the injection of toxin-antitoxin is not yet ascertained. In one series of cases the immunity persisted in 100 per cent. of a group of fifty children for at least twenty-two months. Workers in the Research Laboratory have found that the immunity once acquired lasts for at least four and one half years.

6. It is possible to render a child-caring institution diphtheria free. This has been accomplished for a period of five years at the Home for Hebrew Infants by injecting all susceptibles with toxin-antitoxin mixtures.

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THE EYE IN HEREDITARY SYPHILIS

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INTRODUCTION

It is a truism that no tissue of the body is exempt from the ravages of syphilis, and as no tissue is exempt, so every organ may be invaded by one or more of the multiform manifestations of this disease. This statement applies equally to inherited as well as to acquired syphilis.

So multifarious and far reaching are the aspects of syphilis, both medical and social, that many master minds have deemed the study of this disease worthy of a life time of intense application. Some of the most brilliant deductions on which our present fairly exact knowledge of the disease is based were made by clinicians prior to the discovery of the spirochaeta pallida. Among the many investigators, two names will go down to posterity as the fathers of modern syphilology — Hutchinson and Fournier.

The knowledge that the eye might be affected in syphilis was known to some of the earliest medical writers. Johannes de Vigo, in "Aphrodisiacus" (1567), speaks of "various diseases of the eye which are caused by lues" and gives therapeutic indications. A cure of "ophthalmia gallica" by means of mercury is described by Zacutus Lusitanus (Amsterdam) in 1634.

It is a far cry from these and other early scattered allusions to the formal exposition of the subject of "Diseases of the Eye of Venereal Origin," which was given to the medical world by William Lawrence in 1830. His treatise has now only a historic interest. In those pre-ophthalmoscopic days the intraocular morbid conditions were little known, and a writer could, without fear of contradiction, give rein to any pleasant fancies he might have.

The first description of pigmented and white atrophic areas of choroiditis as a result of syphilis was given in 1856 by Wordsworth.

Bader [1] (1858) noted the presence of small circumscribed white spots in the eye grounds of a patient who had passed through interstitial keratitis. In 1863, Hutchinson [2] described choroidal and retinal disease in hereditary syphilis, and in 1866 [3] he noted the occurrence of optic neuritis in such patients. From this date references to intraocular lesions became each year more and more frequent.

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1. Bader: Ophth. Hosp. Rep., pp. 248-252, 1857-59.
2. Hutchinson: Diseases of the Eye and Ear Consequent on Inherited Syphilis, 1863.
3. Hutchinson: Ophth. Hosp. Rep. p. 307, 1866.

Sidler-Huguenin [4] was able to collate a large number of observations. His paper, which is by far the most exhaustive in the literature, discusses mainly the eye ground changes. He gives a careful summary of papers which have hitherto appeared, supplemented by a very detailed description and classification of the ophthalmoscopic pictures in 125 patients personally observed. Haab [5] has given this aspect of the subject special consideration, and supplements his description of the eye ground changes by several beautiful colored plates. His classification closely resembles that of Sidler-Huguenin. Hirschberg [6] has also considered at length the eye ground changes of hereditary syphilis. Groenouw [7] discusses in a very exhaustive manner, with full references to the literature up to 1904, all the ocular manifestations of hereditary syphilis. As this treatise and the paper of Sidler-Huguenin contain all noteworthy references of the participation of the eye in hereditary syphilis to this date, no attempt will be made to include in the bibliography references prior to 1904.

Allusion should be made to a thesis by Antonelli [8] in which he describes what he terms "Rudimentary Ophthalmoscopic Stigmata" of inherited syphilis. His views, which are presented with great enthusiasm and dogmatism, have received little support, and that mainly from his own countrymen. Sidler-Huguenin, Hirschberg and Haab all speak disparagingly of Antonelli's conclusions. They regard his so-called stigmata either as appearances well within physiologic limits, or representative merely of a vice of nutrition, in which the syphilitic virus may have had an important rôle. They deny in toto that these stigmata are in any sense pathognomonic for syphilis.

OCULAR LESIONS IN HEREDITARY SYPHILIS

The incidence of ocular involvement in hereditary syphilis has been variously estimated. Among 127 cases Rabl [9] found ocular involvement in 39 per cent. Fournier found 48 per cent. of 212 syphilitic children with eye affections. According to the statistics of Ohanian,[10] about 0.5 per cent. of all ocular diseases are caused by hereditary syphilis. His conclusions were based on an examination of 29,528 diseased eyes.

Ocular lesions are rare in the new-born. As a rule, the first signs appear some weeks after birth. The explanation, according to Igers-

4. Sidler-Huguenin: Beitr. z. Augenh. **51**:1, 1902.
5. Haab: Ophthalmoscopy, Am. Ed., 1901, Figs. 39, 40, 41.
6. Hirschberg: Deutsch. med. Wchnschr. **32**:746, 1906.
7. Groenouw: Graefe-Saemisch., 2d Ed. Pt. 1, **22**:804.
8. Antonelli: Thése de Paris, 1897.
9. Rabl: Wien. med. Presse, No. 7.
10. Ohanian: Geneva Thesis, 1894.

heimer,[11] is that the unborn child usually becomes infected in the last months of intrauterine life. Fetuses which were infected earlier either succumb to the infection before birth or soon afterward. In his series of twenty-seven syphilitic nurslings twenty-one had ocular syphilis.

Lids.—The skin of the eyelids may participate in the general cutaneous eruption. Loss of the eyebrows may ensue. It is doubtful whether ulcerative blepharitis ever has a syphilitic basis, although Hutchinson and others have affirmed their belief in this possibility. Inflammation of the tarsus yielding readily to specific treatment has been observed in early infancy. Progressive enlargement of the tarsus is described by Basso[12] in two cases. In one the tarsus had attained the size of a pigeon's egg at the end of the seventh year. The removed mass showed hyaline degeneration of the cartilage and well-marked endarteritis obliterans.

Conjunctiva.—The specific lid eruptions are often accompanied by conjunctivitis. Igersheimer[11] is convinced of the existence of a true syphilitic conjunctivitis, which clears up under general and without local treatment. Hemorrhage from the conjunctiva, sometimes uncontrollable and leading to death, has been observed in infants the victims of hemorrhagic syphilis of the newborn. Syphilitic papules, granulomas, gummas and ulcers may have their seat on the conjunctiva. Essential shrinkage of the conjunctiva may be an end-result of syphilitic pemphigus. In a boy, aged 15, with late hereditary syphilis, Speciale-Cirincione[13] found a conjunctival growth which had all the histologic structure of gumma — perivasculitis with secondary proliferation of connective tissue.

Lacrimal Apparatus.—Infantile dacryocystitis is usually due to blocking of the lower end of the nasal duct with a plug of fetal detritus. However, true syphilitic periostitis of the nasal duct accompanied by specific inflammation of the sac occasionally occurs. Wood[14] examined pathologically the lacrimal glands from ten syphilitic children and found that all bore evidence of disease similar to that found in other glandular organs of syphilitics.

Cornea and Sclera.—The occurrence of parenchymatous keratitis as an incident of hereditary syphilis was known to early writers, some of whom, however, regarded "scrofula" as the most frequent cause of this disease. After Hutchinson had presented his triad of symptoms pathognomonic of hereditary syphilis — misshapen teeth, nerve-deaf-

11. Igersheimer: Ophthalmoscope **11**:718, 1913.
12. Basso: Ann. di Ottal. **29**:645.
13. Speciale-Cirincinone: Rev. gén. d'opht. **22**:145, 1903.
14. Wood: Med. Sentinel **13**:157, 1905.

ness, and interstitial keratitis—the latter acquired a greater importance as a diagnostic sign in the eyes of clinicians. Of late years a fourth symptom has been added to the triad, viz., arthritis, which has often been found associated with interstitial keratitis. Thus Puech,[15] in twenty-seven patients with interstitial keratitis, found eleven with joint disease.

Can interstitial keratitis occur in the offspring of hereditary syphilitics? In none of the reported cases can one exclude with certainty the possibility of acquired syphilis in the parents or child (extragenital postpartum infection). A well-authenticated case has recently been reported by Strezeminski.[16] On the other hand, Sidler-Huguenin found no syphilitic eye disease in nineteen children of hereditary syphilitic parentage.

Interstitial keratitis has generally been regarded as the most frequent ocular complication of inherited syphilis. Statistics of various authors indicate an incidence of from 6.5 per cent. to 96 per cent. (average in 2,000 cases, 50 per cent.). As is well known, the disease occurs almost exclusively in late hereditary syphilis. Very rarely the cornea is found involved at birth or the disease shows itself in the first days of life (Igersheimer).

The frequent association of keratitis with retinochoroiditis is well established. The time of the occurrence of this complication is usually after the subsidence of the keratitis. It may precede it.

Interstitial keratitis is almost always bilateral, although the eyes are not usually attacked simultaneously. The disease seems to show a slightly greater predilection for females. As is well known, a slight trauma may be the exciting cause. Vigorous specific treatment instituted to cure a unilateral syphilitic keratitis will not usually prevent the development of the disease in the fellow eye or relapses in the eye first attacked. On the other hand, intensive and prolonged treatment of a syphilitic infant prior to the appearance of keratitis will usually prevent its development in either eye.

Very rarely other types of corneal disease have been observed. Groenouw cites Kerabutsi and Outsi,[17] who observed punctate keratitis, and Sendziak [18] who reports sclerosing keratitis. Neuroparalytic keratitis dependent on disease of the trigeminus was noted by Fromaget.[19] Keratomalacia has been observed in very greatly emaciated children. Peltesohn [20] reports two cases cured by specific treatment. Fuchs [21]

15. Puech: Bull. et mém. Soc. fran. d'opht. **21**:709, 1901.
16. Strezeminski: Archiv. f. Ophth. **53**:360, 1901.
17. Kerabutsi and Outsi: Ophthl. Klinik 7:118.
18. Sendziak: Rev. hebd. de laryngol., No. 2.
19. Fromaget: Thése de Paris.
20. Peltesohn: Deutsch. med. Wchnschr. **24**:286, 1898.
21. Fuchs: Ophth. Rev., London **28**:247, 1909.

has recently noted the occurrence of vertically oval cornea in hereditary syphilis. Of twenty-eight cases observed, fourteen had interstitial keratitis. He concludes that vertically oval cornea is relatively more frequent in hereditary syphilis and seems to be the precursor of interstitial keratitis. Distention of the scleral and corneal tissues through increased intraocular tension may lead to megalophthalmos, as in a case reported by Arning.[22]

Muscles. — Paralysis of the intrinsic and extrinsic muscles and paralysis of the trigeminus have been observed. The oculomotor and abducens may be partially or completely paralyzed. A unilateral internal ophthalmoplegia is almost certainly due to syphilis. Igersheimer has reported eight cases of nystagmus without ophthalmoscopic signs in syphilitic babies; improvement or cure took place under specific therapy. Zappert [23] has observed a complete ophthalmoplegia as the sole manifestation of tardy hereditary syphilis.

Whether or not concomitant strabismus bears any relation to hereditary lues is an undecided question. Antonelli observed squint in 50 per cent. of children with hereditary syphilis. Statistics from other authors indicate a lower incidence.

Iris and Ciliary Body.—Iritis, which was first described as an ocular complication by Lawrence, is infrequent as compared with the occurrence of the disease in acquired syphilis. Sidney Stephenson [24] says: "The disease must be exceedingly rare, for I cannot recall in my work having recognized a single case." It may be present at birth. Owing to the lack of systematic examination of syphilitic infants' eyes, it is probable that we do not, at the present time, know even approximately the true incidence of this disease. Usually of a "quiet" type, it gives rise to few of the classic symptoms and may run its course without the parent suspecting ocular disease. In the absence of marked ciliary congestion and pain, discoloration of the iris and sluggishness or immobility of the pupil are the important diagnostic signs. Not rarely a mydriatic will reveal synechiæ in cases with very slight clinical signs. Serous iritis with deposits on Descemet's membrane has been described. The disease may also simulate the nodular or gummatous iritis of adults. Recently Igersheimer [11] has described what he calls "syphilitic pseudoglioma." A severe plastic inflammation of the iris and ciliary body results in the filling of the pupil with a yellowish mass which soon becomes covered with vessels. This is apt to

22. Arning: Deutsch. med. Wchnschr. **36**:289, 1910.
23. Zappert: Arch. f. Kinderh., **19**:161, 1895.
24. Stephenson: Ophthalmoscope **4**:506, 1906.

result in closure of the pupil with secondary glaucoma. A gumma of the ciliary body, appearing as a round red boss 10 mm. behind the corneal margin, has been described by Panas.[25]

Lens.—Clouding of the lens is for the most part secondary to disease of the uvea or retina. Posterior polar cataract in a syphilitic brother and sister with diffuse retinitis is reported by Riegel.[26] Zonular cataract is stated by Bull [27] to be usually of syphilitic origin.

Vitreous.—Many cases of retinochoroiditis are associated, at least in the beginning, with vitreous haze, which may seriously interfere with vision. Sidney Stephenson [24] describes a form of amblyopia in children due to opacities in the vitreous. The individual particles are usually so small that they cannot be distinguished. Fluctuation in sight is an important diagnostic point. He believes that in children "a cloudy vitreous humor means one thing only — the existence of congenital syphilis."

Eyegrounds.—Disease of the eyeground in hereditary syphilis was first described by Bader [1] and Drognat-Landré.[28] The literature contains a large number of isolated observations, but there was little attempt at classification until the exhaustive treatise of Sidler-Huguenin [4] appeared. This monograph of 256 pages (1902) contains a very complete summary of the literature, together with a detailed account of the general physical and ophthalmoscopic findings in 125 hereditary syphilitics. On the basis of this study this author has divided the retinochoroidal changes in hereditary syphilis into four types, as follows:

Type I: Innumerable fine, roundish, yellowish-red dots, intermingled with equally fine brown or black pigment dots, comparable to black pepper sprinkled over a yellowish red background. This mild form is often present only in one quadrant of the fundus. The peripapillary zone and macula are not often involved. The disk may be normal or pale, but is not atrophic. Vision is usually normal. In more pronounced cases the pigment spots may be large and angular and approach or invade the macula. The nerve is pale — partial atrophy. The retinal vessels are narrowed. Vision is poor. The changes all lie in the retina.

Type II: Larger pigment masses, isolated or confluent, are situated at the periphery. Between these masses are round, reddish-yellow foci which are not so numerous as the pigmented ones. They show little tendency to merge. The disease is situated primarily in

25. Panas: Arch. gén. d'Opth., 1902.
26. Riegel: Münch. med. Wchnschr. **54**:546, 1907.
27. Bull: Med. Rec. **73**:594, 1908.
28. Drognat-Landré: Ann. d'Ocul., 1875.

the choroid. The nerve may undergo partial or complete atrophy. Sometimes the eyeground between the areas is a leaden hue, traversed by bands of connective tissue. Type II is often found after the subsidence of interstitial keratitis.

Type III: Consists of round or oval, light-colored areas, usually situated at the periphery. They may extend back toward the posterior pole. Some of the areas remain small; others coalesce and become very large. Prolongations may extend toward the posterior pole. Bordered by pigment, the areas themselves may become lightly pigmented. The disease is probably situated for the most part in the choroid. To this type belongs choroiditis alveolaris. Vision is impaired only when the macula is involved.

Type IV: Bears a striking resemblance to retinitis pigmentosa; cannot, indeed, always be differentiated from it. The nerve-head is atrophic, with narrowed vessels. The pigment masses are more rounded and larger than in retinitis pigmentosa, and alternate with yellowish-red and gray-white atrophic spots. The peripapillary zone is leaden hued. Vision and light sense are diminished.

Three colored plates, illustrating, respectively, Types I, II and III, are given by Haab.[5] As his descriptions of these different appearances are very clear, it has seemed worth while to reproduce them. Of Figure 39, representing Type I, Haab has this to say: "The periphery in the lower left-hand portion of the picture presents a leaden hue, and coal-black circular and triangular pigment patches. The rest of the eyeground is covered with minute yellowish-red spots. The yellowish-red rounded spots stand out from the brown dotted background, which looks as if it were sprinkled with snuff. The retinal vessels are rather small and the optic nerve somewhat discolored. Sometimes the sprinkling is found only in the periphery of the eyeground. But whenever this sprinkling is at all well marked, it indicates hereditary lues."

Figure 40, representing Type II, is thus described: "The disease is often confined for a long time to the periphery. . . . The pigment patches are probably, for the most part, situated in the retina, and are caused by a disease of the pigment epithelium. I am unable to decide whether the pale linear and circular yellowish patches are situated in the choroid or in the pigment epithelium. They may be situated in one or the other. This and the following form of the disease are not rarely found after a diffuse interstitial keratitis if, after the cornea has become sufficiently cleared up, the periphery of the eyeground is carefully examined. In some cases the patches may be confined to one side; in others they may be scattered more or less over the entire eyeground and on both sides. In the case here presented there had been a keratitis."

Of Figure 41 he says: "In place of the black and gray patches which predominate both in size and number in the foregoing picture, we find in some cases only whitish, also circular, and often confluent patches. The larger of these are undoubtedly situated in the choroid. This is shown in the figure by the oval white patch traversed by a red vessel. It is a choroidal vessel, hence the choroidal tissue near the vessel is absent and the white of the sclera shows through. There is no doubt, however, that the pigment epithelium of the retina has disappeared at the site of the patches and is slightly increased about their margins, so that the margins appear somewhat darker than the surrounding tissue. This condition also followed an attack of parenchymatous keratitis. Occasionally the forms shown in Figures 40 and 41 are associated, resulting in a mixture of both dark and light circular confluent patches at the periphery, while sometimes in addition we find the form shown in Figure 39, viz., minute red and yellow spots on a brown mottled background, with a sprinkling of small pigment patches. In general, these three types of hereditary specific eyeground disease show a tendency to the formation of spheric foci, which coalesce and form irregular figures."

Most of the intraocular lesions of hereditary syphilis may, according to Hirschberg,[6] be placed in one of the following four groups: First: Anterior hyalitis, consisting of fine, dust-like opacities. Second: The nerve-head is covered with a delicate veil gradually fading into the surrounding retina. Under treatment the veil may disappear, although the nerve-head never regains its "virginal" tint. Some cases recover, but with connective-tissue formation on the disk. Third: The macular region presents a uniformly brown discoloration. Fourth: The fundus is strewn with countless small, light-colored areas, more numerous near the periphery. There is frequently a pigment dot in the center and pigment massing along the border.

It is often a difficult matter, even for the most experienced ophthalmoscopist, to determine with certainty whether a given appearance signifies a pathologic state or is merely a deviation from the physiologic. For instance, the tint and outline of the nerve-head, the course and caliber of the vessels, the color and texture of the macula, the amount and character of pigmentation in the periphery all vary, and sometimes widely, within physiologic limits. What to one observer may have significance, either as a deviation from the normal sufficiently wide to be considered pathologic, or as a special stigma of a constitutional vice, may, to another, be wholly within physiologic bounds.

Whether there exist veritable ophthalmoscopic stigmata of hereditary syphilis or not, there was not wanting an Italian, A. Antonelli,[8] to assert with conviction that such stigmata existed, and to defend his

position in a thesis presented before the Faculty of Medicine of Paris. Antonelli believes that certain ophthalmoscopic appearances which ordinarily have been classified as physiologic deviations, have true significance as stigmata of hereditary syphilis. He says: "Les lesions du fond de l'oeil comptent parmi les manifestations les plus frequent de la syphilis congenitale, et que ces signes ophtalmoscopiques sont souvent les seules qu' il soit possible de reconnaitre d'emblee, si l'on est prevenu de la chose et si l'on est assez rompu aux finesses de l'ophtalmoscopie."

Rudimentary ophthalmoscopic stigmata are, according to Antonelli's definition, "lesions which cause no functional disturbance, are not likely to be discovered in the ordinary routine of examination, and are so insignificant that they may readily pass unperceived by the ophthalmoscopist."

These stigmata concern: 1. The color, margins and vessels of the disk. 2. The appearance of vessels as they pass over the disk margin and in the peripapillary zone. 3. Color and pigmentation of the peripapillary and central areas. 4. Alterations in the center, equator and periphery of the eyeground.

The following is a synopsis of these stigmata: The papilla is pale or gray over all, or in sectors; the margin is veiled. A pigment mass ("cadre pigmentaire") bordering the disk is sharply defined on the side of the disk and shades off to the retina. The arteries are narrowed, the veins are full. There are irregularities of caliber. The vessels on and near the disk are partially obscured. In the peripapillary region there exists: (1) Retinal edema, often limited to the space between two vessels; (2) a typical slate color, shading off toward the equatorial region. There may be punctate pigmentation, which, when situated peripherally, bears resemblance to pigmentary degeneration of the retina.

It is not surprising that Antonelli's dicta have failed to find widespread support. Most ophthalmoscopists can hardly bring themselves to regard a choroidal pigment ring or regional obscurations of vessels as significant of syphilis or any other disease. On the other hand, the gray nervehead and the brown punctate pigmentation are appearances that all other observers have noted, and they doubtless have a real significance. A careful critique of Antonelli's work was made by Herbout,[29] who divides these stigmata into two categories: 1. Those which are only modifications of the pigment epithelium — choroidal ring, and slate color of the peripapillary region. They have no more significance than irregularities of pigment distribution in the skin,

29. Herbout: Thése de Paris, 1900.

hair, or iris. They are simply marks of degeneration. 2. Those which are indications of past optic neuritis; pallid disk with obscured borders, narrowed arteries and voluminous veins.

Disease of the retinal vessels (arteries, veins, capillaries) is indicated by the development of perivascular white lines and eventually by the transformation of the vessels into solid white strands. Retinal hemorrhages or choroidal atrophic areas may be associated with the diseased vessels. Under specific treatment the vessels may be restored to normal. Oliver [30] has described a rare type of perivasculitis in which the arteries and veins were exceedingly dilated. Igersheimer notes the frequency of a pale silver gray tint of the optic disk, which probably is the intraocular expression of a high-grade anemia. One such nerve examined histologically showed neither inflammation nor degenerative changes.

Primary optic neuritis occurs in hereditary as well as in acquired syphilis, and may result in secondary optic atrophy. Heine [31] insists that optic neuritis is very common in syphilitic infants. His material, from Neumann's clinic, indicated that of 105 syphilitic babies, 86 (81.9 per cent.) had optic neuritis. He asserts that optic neuritis may be the sole sign, in addition to a positive Wassermann, of hereditary syphilis, and hence that it has great diagnostic significance. This very large percentage has not been found by other observers. It is questionable whether a primary atrophy occurs. There seems good grounds for believing that tabetic optic atrophy may occur (Lervit [32]).

It is important to note that eyeground changes may escape observation for the reason that usually they give rise to no symptoms. Very rarely is the infant so blind that he cannot grasp at toys and in other ways comport himself as a normal child, so that only by a systematic examination of the eyeground of every syphilitic child will these changes invariably be brought to light.

Orbit.—Periostitis of the orbit, involving, as a rule, the upper part of the orbit, has been noted in hereditary, as well as in acquired, syphilis. Pain and exophthalmos are prominent symptoms. Optic neuritis or choking due to interference with the venous return may occur. Sometimes the process goes on to pus formation. Tumors and tuberculosis of the orbit must be excluded.

Miscellaneous. — Primary glaucoma has never been observed. Increased tension may occur as an incident in the course of retinochoroiditis or iritis. Congenital anomalies, such as microphthalmos,

30. Oliver: Tr. Am. Ophth. Soc. **11**:265, 1906-1908.
31. Heine: Jahrb. d. Kinderh. **72**:328, 1910.
32. Lervit: Thése de Berlin, 1906.

coloboma of the iris, corectopia, congenital cataract, ectopia lentis, defects of the lens, and choroidal coloboma have been ascribed by some authors to hereditary syphilis.

PATHOLOGY

A consideration of the pathology of the ocular lesions of hereditary syphilis is outside the scope of this paper. A very complete summary, up to 1902, of the rather scanty literature bearing on the pathology of retinal, choroidal and optic nerve lesions is given by Sidler-Huguenin (p. 30). (For a systematic discussion the reader is referred to Parsons, Pathology of the Eye, 1904, vol. i, pp. 5, 78, 191, 278, 294, 354; vol. ii, pp. 406, 434, 461, 615, 683.)

The present study was undertaken to gain some conception of the extent to which the ocular tissues participated in the lesions of inherited syphilis. The work was entered into with an open mind and without knowledge of the results of similar studies which had previously been published

The material came exclusively from the Pediatric Clinic of Washington University and the wards of the St. Louis Children's Hospital. A number of these patients applied primarily to the eye clinic and were referred to the pediatric clinic for diagnosis and treatment. It is believed that the 100 cases fairly represent the types of hereditary syphilis seen in a pediatric service, and that the number and kinds of ocular complications are what might be expected in such a group.

No child was included in whom the clinical diagnosis of hereditary syphilis was not confirmed by at least a 2 plus blood Wassermann. In forty-eight children a spinal fluid Wassermann was made in addition. To the best of my knowledge the present is the only ocular study in which the clinical diagnosis has been confirmed in every case by a serologic test. The examination of each child's eyes was conducted systematically and recorded on a prepared blank, which included the following points to be investigated: 1. Name. 2. Age. 3. Sex. 4. Color. 5. Clinical diagnosis. 6. Localization of syphilitic lesions. 7. General complications (non-syphilitic). 8. Blood Wassermann. 9. Spinal fluid Wassermann. 10. Pupils (size, equality, reactions). 11. Ocular muscles (strabismus; paralytic or concomitant; internal or external). 12. Conjunctiva. 13. Cornea (clear, nebula, leukoma, keratitis, salmon patch, ulcer, vascular remains). 14. Descemet's membrane (deposits). 15. Anterior chamber (clear, cloudy). 16. Iris (color, iritis, synechiæ). 17. Lens. 18. Vitreous. 19. Eyegrounds (disk, arteries, veins, perivasculitis, edema, exudate, hemorrhage, pigmentation, depigmentation). 20. Ophthalmoscopic diagnosis (full description).

Analysis of Eye Findings in One Hundred Cases of Hereditary Syphilis

No.	Age, Yrs.	Sex and Color	Pupils	Muscles	Cornea	Iris	Eyegrounds	B. W.	S. F. W	Clinical Diagnosis	Remarks
1	13	F W	R. > L., react	.....	.....	Hazel	R., disk hyperemic, margins veiled; small round clumps of hyperpigmentation alternating with areas of depigmentation; L., the same	+++	—	Hereditary syphilis	V. R. E., 6/5; V. L. E., 6/5; nerve deafness
2	11	M W	Equal, react	.....	Both nebulous from former keratitis	R., gray; L., piebald	R. and L., lower periphery punctate with fine brown dots	+++	—	Latent hereditary syphilis	Eyes very sore at age five
3	9	F W	Equal, react	.....	.....	Hazel	R. and L. normal.....	++	—	Hereditary syphilis	
4	10 mos.	M W	R. and L., miosis, react	.....	.....	Hazel	Both disks pale, margins veiled; retina very pale, vessels narrowed	++++	—	Hereditary syphilis	Square rachitic head; spleen enlarged
5	10	M W	Equal, react	.....	R., nebula below; L., dots of central infiltration	Blue	R., disk veiled above; L., upper and nasal margins obliterated, retinochoroidal spots	++++	—	Hereditary syphilis	V. R. E., 6/8; V. L. E., 6/5
6	8	F W	L. > R., L. fixed	.....	.....	Hazel	R. and L., partial optic atrophy, perivasculitis; "peppered" generally; macula presents larger pigment clumps overlying retinal vessels	++++	0	Syphilitic spastic paraplegia	Partial optic atrophy with disseminated chorioretinitis; marked tendency for pigment to wander together in clumps
7	1	F Col.	Equal, sluggish	.....	.....	Brown	Both disks pale; irregular peppering tending to clumping	++	0	Hereditary syphilis	Mother states baby's eyes weak in bright light; small and undernourished
8	9	M Col.	Equal, react	.....	.....	Brown	R. and L. normal.....	++	—	Hereditary syphilis	Subjectively well
9	1½ mos.	F W	Equal, react	.....	.....	L., iritis, synechia up	R., disk pale; veiled; arteries narrow; veins full; L., red reflex only	++++	++++	Hereditary syphilis	R., post. neuritic atrophy; L., iritis, hyalitis; died of bronchopneumonia
10	1 mo.	M W	Equal, react	.....	.....	Hazel	R., disk pale; veiled; veins full, not tortuous; L., "peppered" fundus, marked at macula; veins full, not tortuous	++++	0	Hereditary syphilis	
11	5	F W	Equal, react	R., external squint; not paralytic	.....	Hazel	R., optic atrophy; L., normal	+++	0	Hereditary syphilis	Rapid lateral nystagmus; at times eyes are quiet; idiocy; carious teeth, pyorrhea
12	5	F W	Equal, react	.....	.....	Brown	R. and L. normal.....	++++	—	Hereditary syphilis	Pertussis; chronic bronchitis
13	11 mos.	F W	Equal, react	.....	.....	Gray	R. and L. normal.....	++++	—	Hereditary syphilis	
14	7	F W	Equal, react	.....	R. and L., interstitial keratitis	Brown	R. and L. normal.....	++++	0	Hereditary syphilis	Old poliomyelitis; residual paralysis

15	5	M	W	Equal, react	.....	R., small infiltration	Hazel	R., disk decidedly pale; L., normal	++++	0	Hereditary syphilis	Premature infant; poor nutrition
16	3	M	W	Equal, react	.....	.....	Brown	R. and L. normal.....	++++	—	Hereditary syphilis	Evidence of former rachitis
17	1	M	W	Equal, react	.....	.....	Brown	Both disks very much congested; margins veiled	++++	0	Hereditary syphilis	Rachitis
18	2	M	W	Equal, react	.....	.....	Hazel	Both fundi "peppered"	+++	0	Hereditary syphilis	
19	1	F	W	Equal, react	.....	.....	Brown	Choroidal rings; uneven distribution of pigment at macula	++	—	Hereditary syphilis	Pulmonary tuberculosis
20	3	F	W	L. > R., L. fixed	.....	.....	Gray	R., nerve head pale, margins veiled; numerous round masses consisting of a pigment ring surrounding a depigmented annulus; center of each frequently occupied by a gray pigment spot; interpigmented spaces are "peppered"; L. the same	++++	++++	Cerebral syphilis	Hemiplegia
21	9	F	W	Equal, react	.....	.....	Gray	R., temporal margin of disk and adjacent retina edematous; disk pale; L., the same; in addition, diffuse pigmentation of retina	++++	0	Cerebrospinal syphilis	Hemiplegia, right cortex
22	10	M	W	Equal, react	.....	.....	Hazel	R., optic neuritis; tortuous veins; L., optic neuritis with peppering lower part of fundus	++	0	Hereditary syphilis	Postpharyngeal membrane
23	14	F	W	L. > R., L. fixed	.....	R., temporal nebula; L., small nebula	R., iritis; brown	R., disk atrophic; vessels extremely attenuated; rounded pigment masses in macula; L., chorioretinitis; rounded pigment masses in upper retina; vessels attenuated	++++	—	Hereditary syphilis	Paralytic mydriasis; no other clinical signs
24	8	M	W	Equal, sluggish	R., partial ptosis	.....	Gray	R., disk pale; margins veiled; L., disk slightly pale; margins better defined	++++	++++	Cerebrospinal syphilis	Mental deficiency
25	12	F	W	Equal, react	.....	R., keratitis; L., old vascular remains	Hazel	R. and L. normal.....	++++	—	Hereditary syphilis	Gumma wall of pharynx
26	6	F	Col.	Equal, react	Internal strabismus	.....	Brown	L., retinochoroidal atrophy upper part of fundus; R., normal	++++	++++	Cerebrospinal syphilis	

ANALYSIS OF EYE FINDINGS IN ONE HUNDRED CASES OF HEREDITARY SYPHILIS—(*Continued*)

No.	Age, Yrs.	Sex and Color	Pupils	Muscles	Cornea	Iris	Eyegrounds	B. W.	S. F. W.	Clinical Diagnosis	Remarks
27	6	M W	R., very sluggish; L., 3.5 mm.; react	.....	.....	Gray	Optic neuritis; both maculae very granular	++++	++++	Hereditary syphilis	
28	10	M W	Equal, react	.....	.....	Brown	R., congested disk; edema of retina to nasal side; L., optic neuritis; several minute retinal hemorrhages	++	0	Hereditary syphilis	Bronchitis
29	6	M W	L. > R., sluggish	.....	.....	Brown	R., neuroretinitis punctata; periphery finely "peppered"; L. the same	++++	+++	Cerebrospinal syphilis	Paresis (?)
30	6	F W	Equal, react	.....	.....	Hazel	R. and L., "peppered" fundus; R. shows irregular pigment distribution at temporal margin	+++	0	Hereditary syphilis	Pulmonary tuberculosis
31	10	M W	Equal, react	.....	.....	Brown	R. and L. normal.....	++++	++++	Cerebrospinal syphilis	Idiocy
32	13	M W	Equal, react	.....	.....	Blue	R., temporal pallor, obscuration of nasal half of disk; splotches of retinal pigment around disk, granular macula; L., the same	++++	0	Hereditary syphilis	Orthostatic albuminuria
33	13	F W	Equal, react	.....	.....	Blue	R. and L., congested disks; brown punctation in maculae	++++	0	Hereditary syphilis	Slightly feeble minded
34	2	M W	Equal, react	.....	.....	Blue	R. and L. macular regions look as though dusted with pulverized pepper	++++	0	Hereditary syphilis	
35	13	F W	Equal, react	.....	R., central scar from exposure	R., iritis	R. and L. normal.....	++++	0	Hereditary syphilis	Large syphilitic ulcer of frontal region; lower eyelid destroyed by ulceration
36	14	M W	Equal. react	.....	.....	Hazel	R. and L., marked retinal haze; R., depigmented area bordered by pigment	++++	0	Hereditary syphilis	Gumma of liver
37	8	F W	Equal, react	.....	Both, old interstitial keratitis	Brown	R. and L. normal.....	+++	—	Hereditary syphilis	
38	6	M W	Equal, react	.....	R. and L., nebulae	Hazel; L., iritis	R., upper and lower periphery show a few patches of depigmentation	++++	0	Hereditary syphilis	
39	13	F W	R. > L.; R., sluggish	.. ..	.. ..	Brown	R. and L. normal.....	++++	—	Hereditary syphilis	L., posterior polar opacity; mental deficiency

40	11	M	W	Equal, react	.....	.....	Hazel	R. and L., partial optic atrophy	++++	0	Hereditary syphilis	Chronic bronchitis
41	4 mos.	M	W	Equal, react	.....	.....	Hazel	R. and L. normal.....	++++	++++	Hereditary syphilis	Dermatitis; diarrhea
42	8 mos.	F	Col.	Equal, fixed	.....	.....	Gray; L., ectropion uvea	R. and L. normal.....	+++	—	Hereditary syphilis	Very rapid nystagmus — about 150 oscillations a minute
43	9	F	W	Equal, react	.....	.....	Hazel	R. and L., disks very red; fine pigmentary deposits throughout	++	—	Hereditary syphilis	R., ptosis; arthritis of knee; V. R. E., 6/12; V. L. E., 6/5
44	9	M	W	Equal, react	.....	R. and L., nebula from old interstitial keratitis	Brown	R. and L., probably normal; corneal haze	+++	—	Hereditary syphilis	Marked rhagades at oral angles
45	9	M	W	Equal, react	.....	.....	Brown	R. and L., optic neuritis	+++	0	Hereditary syphilis	Osteomyelitis of tibia
46	6	M	W	Equal, react	.....	R., central nebula from old keratitis; L., normal	Gray	R. and L., areas of fine-brown punctation alternating with depigmented spots	++	0	Hereditary syphilis	
47	12	F	W	R. and L., marked hippus	.....	.....	Gray	R. and L., very well-marked choroidal ring; upper part of fundus distinctly peppered; temporal pallor	++++	0	Hereditary syphilis	
48	9	M	W	Equal, react	.....	.....	Hazel	L., disk very hyperemic, with blurred lower border; R., normal	+++	0	Hereditary syphilis	Large square head; facial asymmetry
49	1	F	W	Equal, sluggish	.....	.....	Hazel	R. and L., marked peripapillary pigment punctations	++++	+++	Hereditary syphilis	Malnutrition; sores on body; died
50	2 mos.	M	W	Equal, react	.....	.....	Gray	R. and L., disks slightly pale	++++	0	Hereditary syphilis	Rash on neck, ankles and wrists; epiphysitis; paralysis of both arms
51	9	F	W	Equal, react	.....	R. and L., remains of former keratitis	Blue	R., temporally 6 to 8 round and oval areas of retinochoroiditis; L., 15 to 20 areas of retinochoroiditis in temporal periphery	++++	0	Hereditary syphilis	Saddle-nose
52	3	M	W	Equal, react	Alternating squint	.....	Brown	R. and L., disks pale; entire fundi as though sprinkled with fine black pepper	+++	—	Hereditary syphilis	Idiocy
53	3	F	W	Equal, react	.....	R. and L., beginning keratitis	Hazel	R. and L., optic neuritis; central and peripheral punctate depigmented dots	++++	0	Hereditary syphilis	Arthritis of knee
54	4	F	W	Equal, sluggish	.....	.....	Brown	L., small area of retinochoroidal atrophy down and in; R., normal	++++	++++	Cerebrospinal syphilis	Mental deficiency
55	1	M	W	Equal, react	.....	.....	Hazel	R. and L., partial optic atrophy	++++	0	Hereditary syphilis	Papulosquamous eruption

71	4	M	W	Equal, react	Alternating strabismus	.....	Hazel	R., haze of macula and pale disk; small retinochoroidal spot; "peppered fundus"; L., disk pale and veiled; several retinochoroidal atrophic spots; perivasculitis; thin membrane overlying retinal vessels below	++++	++++	Hereditary syphilis	Remains of hyaloid artery; arthritis right knee
72	2	F	Col.	Equal, react	.....	.....	Brown	R. and L. normal.....	++++	0	Hereditary syphilis	Syphilids on face
73	6 mos.	M	W	Equal, react	.....	.....	Brown	R. and L. normal.....	+++	0	Hereditary syphilis	Has no clinical signs; Wassermann made because mother had syphilis
74	1	F	Col.	Equal, react	.....	.....	Brown	R. and L. normal.....	++	0	Hereditary syphilis	Mother has 4+ Wassermann; had skin rash
75	5	F	W	Equal, react	.....	R. and L., scars from old keratitis	Blue	R. and L., marked choroidal pigment rings	++	0	Hereditary syphilis	Conjunctiva congested
76	7 mos.	F	W	Equal, react	.....	.....	Gray	R. and L. normal.....	++++	—	Hereditary syphilis	Snuffles, palpable spleen rhagades
77	14	M	W	Equal, react	.....	.....	Brown	Both disks very pale.....	++	0	Hereditary syphilis	
78	11	M	W	Equal, react	.....	.....	Hazel	R. and L., fundus mottled; L., perivasculitis	++	0	Hereditary syphilis	R. and L., anterior hyalitis
79	9	F	W	Equal, react	.....	.....	Hazel	Disks pale and filled in; Round dense black pigment areas, apparently in retina, in places overlying retinal vessels; macular regions punctate with dark pin-point pigmentation	++++	0	Hereditary syphilis	Extreme nervousness
80	7 mos.	F	W	Equal, react	.....	.....	Blue	R. and L. normal	+++	0	Hereditary syphilis	
81	5 mos.	M	Col.	Equal, react	.....	.....	Hazel	Examination unsatisfactory; apparently normal	++++	0	Hereditary syphilis	Eruption on trunk and face
82	11	F	W	Equal, react	.....	.....	Hazel	Both disks pale; edematous; also peripapillary edema	++++	+	Hereditary syphilis	
83	5	F	W	Equal, react	.....	.....	Hazel	R. and L. normal.....	+++	0	Hereditary syphilis; latent	
84	3 mos.	M	W	Equal, react	.....	.....	Hazel	R. and L. normal.....	++	0	Hereditary syphilis	Anal condylomata conjunctivitis
85	6	M	W	R. > L. react	.....	.....	Gray	Finely granular, probably physiologic	++++	0	Hereditary syphilis	
86	8	M	W	Dilated, equal, sluggish	.....	.....	Hazel	Both fundus peripheries evenly punctate with dark brown dots	++++	0	Hereditary syphilis	

ANALYSIS OF EYE FINDINGS IN ONE HUNDRED CASES OF HEREDITARY SYPHILIS—(*Continued*)

No.	Age, Yrs.	Sex and Color	Pupils	Muscles	Cornea	Iris	Eyegrounds	B. W.	S. F. W.	Clinical Diagnosis	Remarks
56	8	F W	Equal, react	.....	R. and L., nebula from antecedent keratitis	Brown	Both disks very pale; peripapillary edema below; both peripheries diffusely peppered	++++	0	Hereditary syphilis	Nerve-deafness
57	3	M W	Equal, react	.....	.....	Hazel	R. and L. normal.....	++	—	Hereditary syphilis	
58	5	M W	Equal, react	.....	.....	Brown	R. and L., marked peripheral peppering	++++	++++	Hereditary syphilis	Rash on trunk
59	1 mo.	M W	Equal, react	.....	.....	Hazel	R. and L. normal.....	+++	0	Hereditary syphilis	
60	9	F W	Equal, react	.....	.....	Gray	Both nerve heads much blurred and pale	++++	—	Hereditary syphilis	Chorea
61	9	M W	Equal, react	.....	.....	Gray	Both eyegrounds show, in upper periphery, numerous brown punctations	++++	0	Hereditary syphilis	Maculopapular eruption
62	2 mos.	F W	Equal, react	.....	.....	Hazel	Disks pale, retina very thin, tesselated eyegrounds	+++	0	Hereditary syphilis	Bloody crusts on skin; died
63	2	M Col.	Equal, sluggish	.....	.....	Brown	R. and L., nerves completely atrophic; disk surfaces devoid of blood vessels; sclerosis of peripapillary choroidal vessels	+++	0	Cerebrospinal syphilis	Blind
64	7	F W	Equal, react	.....	R. and L., keratitis	Hazel	L., upper temporal vein greatly dilated; R., normal	++	—	Hereditary syphilis	Condition of left supramacular vessels suggests that at one time there had been retinal hemorrhage
65	2 mos.	F W	Equal, sluggish	.....	.....	Gray	Both disks pale; papillary and peripapillary edema, veins overfull	++	0	Hereditary syphilis	Spleen enlarged
66	5 mos.	M W	R. > L., react	Slight divergent strabismus	.....	Gray	R. and L., marked veiling of papillae and circumpapillary retina	++	—	Hereditary syphilis	Both lower lids are slightly inverted
67	3	M Col.	Equal, react	.....	.....	Brown	Both eyegrounds show marked diffuse pigment punctation	++	++	Hereditary syphilis	
68	7 mos.	F W	Equal, react	.....	.....	Gray	R. and L., marked diffuse pigmentation	+++	0	Hereditary syphilis	Skin eruption
69	3	M Col.	Equal, react	.....	.....	Brown	R. and L. normal.....	++	—	Hereditary syphilis	
70	4	F Col.	Equal, react	.....	.....	Brown	R. and L. normal.....	++++	++	Hereditary syphilis	

The original diagram tabulating results contained columns for recording under these 20 headings. It was found possible and desirable, in the interest of brevity, to omit from the final tables the headings "localization of syphilitic lesions," "general complications," "conjunctiva," Descemet's membrane," "lens," "vitreous," and "ophthalmoscopic diagnosis," and to include in a general heading, "remarks," the occasional abnormality which would have been recorded under the omitted headings. In fully one-third of the cases any visual test was impossible on account of the age of the patient, and hence vision was not taken as a routine.

An examination of this tabulation will show that seventy-four of these children presented definite pathologic conditions in one or more of the ocular tissues or some derangement of ocular function. Some of these conditions, such as interstitial keratitis, immobile pupils, optic atrophy, and certain eyeground changes can with assurance be ascribed to the syphilitic virus. Others, such as concomitant squint and pallor of the nerve-head, may depend on some factor other than syphilis. Cases of this character were not included in the group of seventy-four unless they presented, in addition, definite syphilitic ocular lesions.

The age incidence is shown in the following table:

Under one	17	Seven to eight	3
One to two	7	Eight to nine	9
Two to three	5	Nine to ten	14
Three to four	8	Ten to eleven	5
Four to five	3	Eleven to twelve	4
Five to six	6	Over twelve	11
Six to seven	8		

Sex and Color.—There were forty-eight male children, of whom five were colored, and fifty-two female children, of whom nine were colored. The number of colored children is, of course, too small to permit any conclusions as to incidence or localization of syphilitic disease in the eyes in negroes.

Pupils.—Nine patients showed pupillary inequality. In five, R. pupil > L. pupil. In four, L. pupil > R. pupil. In nine patients the pupils barely reacted to light, and in three there was complete fixity. One patient showed marked hippus.

Muscles.—Two patients had convergent, two had divergent, concomitant strabismus. Alternating convergent strabismus was observed twice. Partial ptosis (unilateral) was seen once. A lateral nystagmus was observed in three patients; in two the oscillations were fairly rapid, but not constant; in one the rate of oscillation was at least 150 to the minute and constant. In one patient, a child nearly blind, there were typical searching movements.

ANALYSIS OF EYE FINDINGS IN ONE HUNDRED CASES OF HEREDITARY SYPHILIS—(*Continued*)

No.	Age, Yrs.	Sex and Color	Pupils	Muscles	Cornea	Iris	Eyegrounds	B. W.	S. F. W.	Clinical Diagnosis	Remarks
87	1	M W	Equal, react	.....	.....	Gray	Both, numerous pigment dots of varying size, alternating with tiny areas of light color	++++	0	Hereditary syphilis	
88	8	M W	Equal, react	.....	R. and L., old scars of keratitis	Brown	Both, peripheral brown and black punctations	++	—	Hereditary syphilis	
89	3	F W	Equal, react	Nystagmus	.....	Gray	R., optic atrophy; several round white circular areas with pigmented center; L., optic atrophy	++++	++++	Cerebrospinal syphilis	Child evidently nearly blind
90	2	F W	Dilated, very sluggish	Searching movements	.....	Hazel	R. and L., optic atrophy	+++	++	Cerebrospinal syphilis	Sees very poorly
91	7	M W	Equal, react	.....	R. and L., remains of antecedent keratitis	Hazel	R. and L., pigment masses of varying sizes and shapes alternating with light areas in upper periphery	++++	—	Hereditary syphilis	
92	9	F W	Equal, react	.....	R., central nebula; L., dense central vascular scar	Hazel L., synechia	R. and L., no view of eyegrounds on account of corneal scars	++++	—	Hereditary syphilis	
93	10	F W	Equal, react	R., convergent squint	R. and L., nebula from old keratitis	Brown	R. and L., numerous yellow white, round, approximately equal, punctations in periphery	++	—	Hereditary syphilis	Nerve-deafness
94	9	F W	Equal, react	.....	.....	Brown	R. and L. normal; myopia	+++	—	Hereditary syphilis; latent	Speech defect
95	8	F W	R. > L., react	.....	.....	Gray	R. and L. normal.....	++++	0	Hereditary syphilis	Poorly nourished
96	13	F Col.	Equal, react	.....	R., scars of antecedent keratitis	Brown	R. and L. normal.....	+++	—	Hereditary syphilis	
97	9	M W	Equal, react	.....	.....	Brown	R. and L. normal.....	++++	0	Hereditary syphilis	
98	8	M Col.	Equal, react	.....	.....	Brown	R. and L. normal.....	+++	—	Hereditary syphilis	Oral ulceration; gum adherent to cheek
99	8	F W	Equal, react	.....	.....	Brown	R. and L. normal.....	++	—	Hereditary syphilis	Papular and vesicular eruption
100	6	M W	Equal, react	.....	.....	Hazel	R. and L., optic neuritis...	+++	0	Hereditary syphilis	

Conjunctiva.—In no case was there a primary conjunctivitis. Conjunctival congestion was present only in patients with active keratitis.

Cornea.—Nineteen patients presented evidences of present or past interstitial keratitis. In seventeen the disease was bilateral. The corneal disease was mostly of a mild type. Some patients who presented indubitable nebulæ had been so slightly incommoded that they, or their parents, denied that the eyes had ever been sore. A beginning bilateral keratitis was observed in a white girl aged 3 (No. 53). In No. 35 syphilitic destruction of the lower lid resulted in keratitis from exposure.

Descemet's Membrane.—In no case were deposits or any abnormality observed.

Aqueous.—The aqueous was slightly turbid in two cases of active iritis.

Iris.—Thirty-six patients had brown irides, thirty-seven hazel, twenty gray, and seven blue. There is, in my opinion, absolutely no connection between the color of the iris and hereditary specific infection. Four patients had mild iritis. In two the condition was unsuspected until the mydriatic, used to facilitate ophthalmoscopic examination, disclosed one or more synechiæ. In the other two there was moderate ciliary injection with cloudiness of the aqueous.

In one patient with an absolutely white eye mydriasis disclosed a synechia which represented an antecedent iritis which had never been recognized and had subsided without local or general treatment.

Lens.—The only abnormality noted was in No. 39, who had a small posterior polar opacity. The periphery of the lens was clear and permitted a good view of the normal eyegrounds.

Vitreous.—Nos. 9 and 78 presented a fine haze of the anterior part of the vitreous. No. 71 showed in one eye remains of the hyaloid artery.

Eyegrounds.—In the ophthalmoscopic examination great care was taken to secure as complete a picture of the eyegrounds as possible, which necessitated, in many cases, repeated examinations under mydriasis. The intraocular lesions of hereditary syphilis are so frequently situated peripherally that an examination confined to the region of the disk and macula would have failed to uncover characteristic ophthalmoscopic changes. The greatest difficulty was experienced with infants, who almost invariably cried and struggled when the light was flashed into their eyes. With the head controlled by the assistant, and the arms and legs firmly pinioned by the nurse, it was usually possible to secure a satisfactory examination. After a short preliminary struggle the infant would become interested in the bright light of the electric ophthalmoscope, and perhaps a little hypnotized by it, and the

examination would proceed in quiet. To secure a view of the periphery, a flashlight brighter than the ophthalmoscopic light would be held to the right, left, above and below, and repeatedly flashed. This manœuver usually succeeded in causing the eyes to rotate in the desired direction, and afforded a satisfactory view of the outlying regions of the retina.

Fifty-two of these 100 children presented undoubted pathologic eyeground lesions. Thirty-seven showed no intraocular lesion, but in a few of this group ophthalmoscopic examination was impossible on account of the density of the corneal opacity. There remain eleven "borderline" cases, which, while showing certain deviations from the normal, did not, in my opinion, present such indubitable evidences of intraocular pathology as to warrant their being placed in the first group. These "probably pathologic" cases presented such signs as undue pallor of the nerve-head without signs of true atrophy, hyperemia of the nerve-head without evidence of true neuritis, a diffuse haze of the nerve-head and surrounding retina without central or peripheral lesions, and a brown pigmentation of the macula without other ophthalmoscopic stigmata. There was hardly a single pathologic eyeground that did not present lesions of diverse types; in other words, mixed forms predominated. The attempt will be made to describe characteristic changes under appropriate appellations. These changes were:

1. Peripheral, sometimes central, punctate pigmentation.

2. Peripheral, sometimes central, punctate depigmentation.

3. Fairly numerous (10 to 30) small (⅛ to ¼ disk diameter), round, whitish areas bordered by gray pigment, often containing a small pigment dot in the center.

4. Small to large, irregular, retinochoroidal atrophic areas bordered by pigment.

5. Small to large masses of gray pigment, usually peripheral, irregularly disposed, and alternating with depigmented areas.

6. Disseminated retinochoroiditis.

7. Sclerosis of choroidal vessels.

8. Neuroretinitis punctata.

9. Retinal hemorrhages.

10. Optic nerve: (*a*) Papillary haze. (*b*) Pallid nervehead. (*c*) Optic neuritis. (*d*) Optic atrophy.

11. Vessels: Perivasculitis.

1. Peripheral and central punctate pigmentation coincides very closely with Type I of Sidler-Huguenin, and is comparable to Figure

39 in Haab's Atlas of Ophthalmoscopy. Twenty-eight patients presented this picture. Tiny dots of brown or brown-black pigment are strewn fairly evenly over the retina. Sometimes the entire fundus is "peppered" — more frequently the distribution is confined to large peripheral areas. The individual dots are round or irregular in outline, and vary somewhat in size. Between the dots are minute yellowish red spots.

These punctate brown dots are so characteristic that after a few cases have been observed it is hardly possible to confuse this picture with any other. As Haab has pointed out, the normal blond eyeground is often punctate with numerous fine gray dots which might be confused with the appearances just described. A point in differential diagnosis is that the syphilitic lesions can be seen with the inverted image, which is not true of the physiologic dotting. The syphilitic lesions, too, are darker, vary more in size, and are more numerous than the physiologic dots.

2. Peripheral punctate depigmentation. This type was much less common. It was observed in only three patients. It was seen typically in No. 93. The periphery of each fundus presented numerous light-colored or even white circular dots. In this case there was no pigment dotting between the light areas. The fundus seemed to have been "rained" upon. In the other two patients these light-colored dots occupied one portion of the periphery, while the other portions were punctate with brown pigmentation.

3. Small round white areas with pigment center and border. This picture was seen in several patients, associated with brown punctations. In No. 20, a victim of cerebral syphilis and hemiplegia (blood and spinal fluid Wassermann, 4 plus), there were numerous small, round, whitish areas with center and border lightly pigmented. These occupied the center of the eyeground. They gave the impression of being superficially situated, probably in the retina.

4. Retinochoroidal atrophy. Five patients presented large, irregular areas of dark, pigment-bordered retinochoroidal atrophy. These bore a striking resemblance to the single, unilateral or bilateral, peripherally situated areas often observed in adults who have never suspected the existence of an ocular lesion. May not a specific intrauterine choroiditis which runs its course be the explanation of many of these unsuspected lesions in adults?

5. Masses of gray pigment alternating with depigmented areas. This appearance was observed in 4 patients, most typically in No. 91. Each periphery was occupied by several large, approximately round, gray pigment masses, one-half to one disk diameter in size. These overlay the retinal vessels. Between them the retina was greatly deficient in pigment.

6. Disseminated retinochoroiditis was observed in two patients, most typically in No. 51. The temporal half of each fundus was occupied by half a dozen or more round, fluffy white areas of active retinochoroiditis. At the time of observation there was no pigment massing along the borders of the lesions.

7. Sclerosis of choroidal vessels. This rare anomaly was observed in No. 63. The sclerosis was confined to the area immediately surrounding the optic nerve, which was completely atrophic.

8. Neuroretinitis puncta was observed in No. 29. The nerve-head was moderately swollen, with very numerous pin-point, glistening white dots occupying the edematous macula.

9. Retinal hemorrhages. Several minute retinal hemorrhages were observed in No. 28, a patient with well-marked optic neuritis. In No. 64 the condition of the vessels above the left fovea was suggestive of an antecedent hemorrhage.

10. Optic nerve.—(*a*) Papillary haze. It was surprising to observe how frequently the optic nerve-head appeared slightly fogged, an overlying veil just sufficient to obscure the details of the disk and obliterate the clean-cut line of demarcation between disk border and retina. This obscuration occurred in some eyegrounds presenting no other abnormal appearances. (*b*) Pallid nerve-head. Nineteen disks, which presented none of the appearances of true atrophy, were included in this group. All these cases were in marasmic or anemic children; the pale disk was probably the intra-ocular expression of the general anemia. (*c*) Optic neuritis. If reference is made to the statistics emanating from Neumann's clinic, it will be seen that the claim is made that fully 80 per cent. of syphilitic nurslings have optic neuritis. The present series showed optic neuritis in only eight patients, or 8 per cent. A quite common appearance in hereditary, as well as in acquired, syphilis is a brick-red disk, without swelling, obscuration of the margins, or vascular alteration. To classify such a hyperemic disk as an optic neuritis, is in my opinion, a serious error. The diagnosis of optic neuritis in children should not be made unless there are obscuration of the margins, slight swelling, and vascular engorgement. (*d*) Optic atrophy. Eight patients presented signs of optic atrophy. In six the atrophy affected both nerves; in two it was unilateral. Three were partial atrophies, five were total. In one unilateral case the other eyeground was normal. In the other the fellow eyeground was involved, presenting a retinochoroiditis. In all of the cases the arteries were contracted and the lamina cribrosa was invisible.

11. Vessels. (*a*) Perivasculitis was observed in Nos. 6, 71 and 78. In the first two it occurred in eyes with optic atrophy. In No. 78 the eyeground was otherwise normal.

SEROLOGIC TESTS

As has been stated, no patient was admitted to the series who did not present at least a 2 plus blood Wassermann. At the time the ocular examinations were begun, about three years ago, it was customary to make serologic examinations of the spinal fluid only exceptionally, and for the most part only on hospital patients. At the present time the spinal fluid of nearly every syphilitic child is subjected to serologic and microscopic tests. For this reason the series includes only forty-eight spinal fluid Wassermanns, of which sixteen were positive and thirty-two were negative. A positive spinal fluid Wassermann always indicates involvement of the cerebrospinal system.

CLINICAL DIAGNOSIS

Eighty-nine cases were diagnosticated as "hereditary syphilis"; nine as "cerebrospinal syphilis"; one as "cerebral syphilis," and one as "syphilitic spastic paraplegia." Many patients were marasmic. Many developed complicating troubles, such as rachitis, bronchitis, bronchopneumonia, pertussis, poliomyelitis, tuberculosis, orthostatic albuminuria, diarrhea, arthritis, osteomyelitis and chorea. Several were deficient mentally.

The results of this study point very clearly to the need of a systematic ocular examination of every syphilitic child. Such an examination may not have great importance from the standpoint of diagnosis, for in this respect the serologic test stands preeminent, but without it the clinical picture may be incomplete. As many of the eyeground lesions are situated primarily in the periphery, it is imperative that treatment be instituted at the earliest possible moment in the hope of preventing an extension of the process to the peripapillary and macular regions. Even if the lesion be central, the outlook for useful vision will be better if the condition be early recognized and treatment controlled by frequent ophthalmoscopic examinations. If optic neuritis is found, it may be unwise to give arsphenamin or any arsenical preparation, and to rely exclusively on mercury, at least until all inflammatory signs in the optic nerve-head have disappeared.

I am convinced that the dark-brown, punctate pigmentation is absolutely characteristic of the eyeground of a hereditary syphilitic. It must be differentiated from the gray punctation seen in many blond fundi, but this is a matter of no difficulty after a few of the syphilitic type have become impressed on the mind.

That occasionally this intraocular lesion may be the sole expression of inherited syphilis, or if others have existed they have been so insignificant that they have been overlooked, is illustrated by the following case:

A boy of 5 was brought to the hospital with fever and symptoms of meningeal irritation. The father was unable to account for the condition, as the child had always been healthy, and there was no reason to suppose that he had been exposed to contagion of any kind. The clinical diagnosis was meningitis. I saw the boy in consultation and found a perfectly typical dark punctate pigmentation of the eyeground and ventured the opinion that the Wassermann on father and child would prove positive, which was actually the case. The child promptly recovered under neo-arsphenamin and mercury.

I have been on the lookout for this type of eyeground disturbance in adults, but have encountered it only twice: Once in a young man of 21 who showed corneal evidences of an old keratitis, and once in a 50-year-old hyperopic woman who presented no signs and gave no history of either inherited or acquired syphilis.

The virus of syphilis is deadly to young human life. Countless babies die before they have ever had a chance to live, and countless more eke out a miserable existence for a few years and then perish. So it is that very few syphilitic children reach adult life, and so it is that the characteristic intra-ocular lesions only rarely show in adults.[33]

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A REVIEW OF THE LITERATURE OF SYPHILIS IN INFANCY AND CHILDHOOD

PART I

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THE INCIDENCE OF SYPHILIS

The statement has recently been made [1] that not a single estimate of the prevalence of syphilis in the general population can stand the test of examination. The reason is that no study has represented a fair cross section of society. The majority of the studies have been made among the sick poor and it is obviously unfair to apply such statistics to the general population. Jeans,[2] from a review of the literature, estimated that in the poorer class from 10 to 20 per cent. of adult males and 10 per cent. of married women are syphilitic. Estimates among adults of the better class vary widely. McLester [3] found 18 per cent. of 567 private patients seen in consultation to be syphilitic. Day and McNitt,[4] in a survey of hospital admissions, found that among the well-to-do 6 per cent. had positive Wassermann reactions. This is contrasted with 13 per cent. in the middle class and 20 per cent. in the poor whites during the same time period. Cornell and Stillians [5] found 3.6 per cent. of pregnant women in private practice to have a positive Wassermann reaction, while in charity hospital practice 10 per cent. of the pregnant women had a positive Wassermann. It seems evident that the higher in the social scale the lower the incidence of syphilis. This naturally has a bearing on the frequency of hereditary syphilis.

Jeans,[2] from a review of the literature, concluded that from 5 to 6 per cent. of the living infants of the poorer class in this country have syphilis. The incidence among older children is lower (from 2 to 3 per cent.) no doubt due to the higher death rate among syphilitic infants. Lacapère and Laurent [6] state that in Morocco scarcely 30 per cent. of the inhabitants escape. Lange [7] found 2.8 per cent. of the total number of children admitted to the Frankfurt

1. Malzberg: J. A. M. A. **73**:1155 (Oct. 11) 1919.
2. Jeans: Am. J. Syphilis **3**:114 (Jan.) 1919.
3. McLester: Am. J. M. Sc. **155**:320 (March) 1918.
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6. Lacapère and Laurent: Paris méd. **8**:422 (Nov. 23) 1918; abstr., J. A. M. A. **72**:280 (Feb. 1) 1919.
7. Lange: Jahrb. f. Kinderh. **90**:83, 1919.

Children's Clinic to be syphilitic. He states that this is similar to other German statistics. In the same clinic 10 per cent. of the adults were syphilitic.

Wirz [8] found 386 syphilitic children among 9,752 admissions to the Munich Children's Clinic in a twelve year period, an incidence of 4 per cent. He also made a Wassermann survey of 200 school children of whom the history and examination were negative as to syphilis. An incidence of 3 per cent. was found. He refers to Saenger who found an incidence of 6.9 per cent. among the new-born in the Munich Obstetrical Clinic. This incidence became 5.9 per cent. when macerated fetuses were excluded. In the pediatric clinic at the same time only from 2 to 3 per cent. of infants had syphilis. However, in the pediatric clinic the Wassermann test was performed only on suspects while Saenger performed it routinely in the obstetrical clinic. Wirz quotes Pfaundler to the effect that but 43 per cent. of the children born living of syphilitic parents reach the age of 10 years, while the normal percentage to reach 10 years is sixty-nine. On this basis, the 3 per cent. at the school age corresponds to 5 per cent. among the new-born. Wirz also thinks that the finding of syphilis in 3 per cent. of unsuspected school children explains the discrepancy between Saenger's figure of 6.9 per cent. in the new-born and the estimate of from 2 to 3 per cent. in the infants of the pediatric clinic.

RELATION OF SYPHILIS TO INFANT MORALITY

From a compilation of the reports of numerous authors Jeans [2] draws the following conclusions: About 75 per cent. of all offspring in a syphilitic family are infected. In a syphilitic family 30 per cent. of the pregnancies terminate in the death of the child at or before term, a proportion three times that which is found in nonsyphilitic families. Thirty per cent. of all children born alive in a syphilitic family die in infancy, a proportion double that which occurs in nonsyphilitic families. Probably from 25 to 30 per cent. of clinically syphilitic infants die as the result of syphilis. Only about 17 per cent. of all the pregnancies in syphilitic families result in living non-syphilitic children who survive the period of infancy.

Lange [7] observed 100 syphilitic infants during a ten year period. Of these sixty-seven died; twenty-four of these were brought to the clinic in a moribund condition. One-fourth of the infants who died were breast fed. Fifty-two died of secondary respiratory and intestinal disturbance. In spite of the disappearance of syphilitic mani-

8. Wirz: Ztschr. f. Kinderh. **19**:189 (July) 1919.

festations, children withstood even mild infection poorly. There were ten premature births in the group and these constituted 10 per cent. of all premature births. Only one of these infants recovered.

HEREDITARY TRANSMISSION

Most, but not all, authorities agree that prenatal transmission of syphilis probably occurs in all instances from the mother to the fetus at some time after conception. Wile [9] gives arguments in favor of a resting stage of treponema pallida, which form would make possible paternal transmission. In such a case he thinks the mother's Wassermann reaction becomes positive because of exchange of antibodies with the fetus. He thinks that paternal infection is the commonest mode of transmission. In the discussion of Wile's paper opinions are expressed by Schamberg, Heiman and Pollitzer. In spite of the fact that Pollitzer believes a spore stage probable, he argues against the possibility of paternal transmission. Schamberg thinks this method of transmission possible; Heiman does not. Gaucher [10] reports a case as one of paternal transmission. The father had had syphilis for three years. He was free from symptoms for two years before marriage. At the age of three weeks the baby developed mouth fissures and anal condylomas. Two months after parturition the mother developed two chancres on the left nipple followed by axillary adenopathy and roseola. Routh [11] believes it possible that the ovum may become infected by the granule stage which develops later. Routh explains the diminishing virulence of infection in successive children on the basis of spirocheticidal action of chorionic ferments, these becoming more effective as the treponemas lose their virulence. The diminishing virulence alone would seem an adequate explanation without his theory. In line with the belief of most syphilographers is the observation of Smith [12] that *Trypanosoma rhodesiensi* can pass directly from the blood of the mother to the fetus in experimental animals. In regard to a spore stage of the *Spirocheta pallida*, Noguchi [13] states that his personal experiences with cultivated strains do not justify such an assumption, except for the fact that *Spirocheta pallida* under cultural conditions is one of the most viable organisms. The organism is unable to pass through any bacteria-proof filters, though under favorable conditions they may grow through such filters in the course of several days.

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12. Smith: J. Trop. M. **22**:198 (Nov. 1) 1919.
13. Noguchi: Am. J. Syphilis **1**:261 (April) 1917.

The behavior of syphilis in plural pregnancies is of some interest. DaCosta and Van der Valk [14] report an instance of twins and one of triplets of syphilitic parentage. Of the triplets, a boy, aged 3 years, has obvious signs; one child died aged 3 weeks without signs, and the third child developed normally. Of the twins, a boy, aged 12 years, has obvious signs, while the twin pregnancy stopped development at the size of an orange. Post [15] cites two sets of twins, all having syphilis. Goldenberg [16] reports the occurrence of syphilis in one of twins and its absence in the other.

Though transmission to the third generation is practically impossible of satisfactory proof, instances of such transmission are reported from time to time. Ash [17] reports a case in which the mother and grandmother of the syphilitic infant had syphilis. The proof is quite unsatisfactory because the father of the baby also had syphilis and the brothers and sisters of the mother were not examined. Murrell [18] reports an instance in which the mother of the infant had syphilis while the father gave a negative Wassermann. The maternal grandparents both had syphilis. The chief fault in this case is that the negative Wassermann of the father means nothing.

THE WASSERMANN REACTION

A review of the various methods of carrying out the complement fixation test for syphilis and their comparative value has not been undertaken. Publications bearing on this subject are very numerous, as are also the proposed methods of carrying out the test. A need for standardization of the test is apparent. A discussion has arisen as to a proper name for the test. Vedder [19] prefers "Bordet-Gengou reaction" for the test now generally carried out; Kolmer [20] prefers to confine the term "Wassermann reaction" to a test with the original technic which is still being used by Wassermann; Gay [21] thinks that Wassermann is entitled to the credit for the development of a novel type of nonspecific fixation of great practical utility. It is quite probable that the common usage of the present will be continued.

All are agreed that the Wassermann reaction, though of great value, should not replace careful clinical examination in any degree. Its value is already so well understood that detailed discussion is not

14. DaCosta and Van der Valk: Urol. & Cutan. Rev. **23**:159 (March) 1919.
15. Post: Am. J. Dis. Child. **12**:364 (Oct.) 1916.
16. Goldenberg: In discussion of paper of Wile, Ref. 9.
17. Ash: Am. J. Syphilis **3**:200 (April) 1919.
18. Murrell: Virginia M. Monthly **45**:285 (Feb.) 1919.
19. Vedder: J. Immunol. **4**:141 (May) 1919.
20. Kolmer: Am. J. Syphilis **4**:166 (Jan.) 1920.
21. Gay: J. A. M. A. **73**:901 (Sept. 20) 1919.

considered necessary. It is generally recognized, that the reaction may be negative in a syphilitic child at birth, and that it becomes positive in the course of a few weeks or months. A strongly positive reaction is present throughout the activity of the disease in childhood. Though the subsidence of activity, with or without treatment, to the point of a negative reaction may and not infrequently does occur, it but rarely occurs in the period of childhood. Several diseases common to this country are reputed to cause positive reactions at times. Tuberculosis is the most frequent example. A serum giving a strongly positive complement fixation test for tuberculosis, because of its high titer and partial nonspecificity, may give a weakly positive Wassermann reaction, especially if a cholesterolized antigen is used. Snow and Cooper [22] found that nonsyphilitic tuberculous individuals may give from partial to complete fixation with cholesterolized antigen in about 31 per cent., but that the percentage giving a positive reaction with noncholesterolized antigen is so small as to be negligible. Complete fixation in the Wassermann reaction is as good evidence of syphilis in the tuberculous as in the nontuberculous.

Malaria, also, is reputed to cause positive Wassermann reactions. Thompson and Mills [23] claim that the test conducted according to a recognized standard does not give a positive reaction in any stage of malaria. If a positive reaction is obtained it is due to undiagnosed syphilis or to faulty technic.

Graves [24] has shown that the Wassermann reaction on serum obtained after death confirmed the antemortem reactions in 97 per cent. of sixty-eight cases. But 2.5 per cent. of the postmortem serums were anticomplementary.

Rusca [25] states that the Wassermann reaction in human milk paralleled that in the blood, except that weak reactions were obtained in colostral milk.

The value of the provocative Wassermann test has been questioned. Stokes and O'Leary [26] found the test of possible benefit in identifying deep seated visceral, osseous or nervous system syphilis in only 27 per cent. of the cases. Its efficiency rose to 40 per cent. in latent cases and to 70 per cent. in late cutaneous and mucous membrane syphilis. It is least valuable precisely where it is most needed, i. e., in obscure visceral, osseous and nervous system infection. Several patients who remained negative showed a symptomatic Herxheimer reaction. This was notably true in the case of periostitis. In their

22. Snow and Cooper: Am. J. M. Sc. **152**:185 (Aug.) 1916.
23. Thompson and Mills: Lancet **1**:782 (May 10) 1919.
24. Graves: J. A. M. A. **70**:1751 (June 8) 1918.
25. Rusca: Pediatria **27**:343 (June) 1919.
26. Stokes and O'Leary: Am. J. Syphilis **1**:629 (July) 1917.

hands, the therapeutic test was obviously superior to the provocative. The efficiency of the provocative test was approximately 18 per cent. as compared to an efficiency of 60 per cent. for the therapeutic test. The test does not yet rest on an uncriticizable foundation. They obtained only presumptive and not conclusive evidence of the existence of a provocative effect, and state that at the best the test yields rather a small return for the amount of labor involved. Pollitzer and Spiegel,[27] in a series of 150 cases of treated syphilis of all kinds, did not find a single clear case of provoked reaction while the assumption of cure in all the cases was obviously untenable. In a series of cases temporarily negative, selected as probably not cured, the provocative test failed to indicate the presence of syphilis though the subsequent course of the cases proved that the syphilis was not cured. They regard the test as a useless and often a misleading procedure.

THE LUETIN TEST

The luetin test has been largely discredited though it is still vouched for by its originator. Stokes[28] was able to produce a similar reaction by means of agar. With the exception of one apparently nonsyphilitic case, normal and nonsyphilitic individuals did not react to agar. Positive reactions were obtained in known syphilitics in from 50 to 70 per cent. He interprets both the luetin and agar reactions as colloidal adsorption phenomena in a hypersensitive or labile skin and as not being specific in character. Apparently, the skin is made more sensitive by the administration of certain drugs. A number of observers have shown that potassium iodid increased the reaction. Cole and Paryzek[29] found the reaction positive or intensified not only in patients taking large amounts of potassium iodid but also in a lesser degree in patients taking sodium bromid, potassium nitrate, calcium bromid and sodium iodid. Others have reported similar results. Stillians[30] and other observers think that a positive test is very useful and reliable in the diagnosis of late cases in which the Wassermann is negative. The test cannot be used in determining a cure because not uncommonly it is negative in latent cases.

The facts mentioned would still leave the luetin test a very useful procedure, provided positive results were not obtained in nonsyphilitic patients who were not taking drugs. That positive results may be obtained in the absence of syphilis has been affirmed by Blechmann[31]

27. Pollitzer and Spiegel: Am. J. Syphilis **3**:252 (April) 1919.
28. Stokes: J. A. M. A. **68**:1092 (April 14) 1917.
29. Cole and Paryzek: J. A. M. A. **68**:1089 (April 14) 1917.
30. Stillians: Interstate M. J. **24**:589 (June) 1917.
31. Blechmann: Arch. de méd. des enf. **18**:197, 1915.

in children, and by Corper, Gekler and Sweaney[32] in adults. The latter found 47 per cent. of the patients admitted to a tuberculosis sanitarium gave positive reactions.

COAGULO-REACTIONS IN SYPHILIS

That syphilitic serum differs from most other serum in regard to the ease with which it can be precipitated has been recognized by a number of observers. Tests for the presence of syphilis based on macroscopic precipitation have been advanced from time to time during the past ten years. A few of these tests discussed in the recent literature are new, others are modifications of methods formerly proposed. Whatever may be the final status of any of the tests it is apparent from them that a large number of syphilitic serums differ in their composition from the majority of nonsyphilitic serums. That there are no protein changes marked enough or of such a nature as to change the index of refraction from the normal has been shown by Vernes and Marchadier.[33]

The simplest of these tests is one decribed by Bruck.[34] It depends on the observation that the precipitate formed on addition of nitric acid to syphilitic serum does not dissolve in distilled water as readily or as completely as in the case of normal or nonsyphilitic serum. The reports[35] to the present indicate that the test is not specific for syphilis. The percentage agreement with the Wassermann reaction is 75 or more. It is apparently of least value in those instances in which it is most needed, the doubtful and weakly positive Wassermann cases.

McDonagh[36] has advanced a "gel" test which consists of the addition of glacial acetic acid to serum, causing the protein to be thrown out as a "gel." The presence of gel is made still more evident by the addition of a sulphate. McDonagh claims that syphilitic serum contains more protein than normal serum and the particles are larger and more numerous. Strickler[37] concludes from his work with the gel test that, though it is a step in the right direction toward finding a simple chemical test for syphilis, it cannot be compared in accuracy to the Wassermann reaction.

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32. Corper, Gekler and Sweaney: Am. Rev. Tuberc. **1**:544, 1917.
33. Vernes and Marchadier: Compt. rend. Soc. de biol. **82**:176 (Feb. 22) 1919.
34. Bruck: Münch. med. Wchnschr. **64**:25 (Jan. 2) 1917.
35. Toyama and Kolmer: J. Cutan. Dis. **36**:429 (Sept.) 1918. Smith and Solomon: Boston M. & S. J. **177**:321 (Sept. 6) 1917. Stillians: J. A. M. A. **69**:2014 (Dec. 15) 1917. Corper and Fiala: Am. Rev. Tuberc. **2**:290 (July) 1918. Farbach: Am. J. Syphilis **2**:292 (April) 1918. Terada: Kitasato Arch. Exper. M. **3**:123 (Oct.) 1919.
36. McDonagh: J. Cutan. Dis. **35**:222, 1917.
37. Strickler: J. Cutan. Dis. **35**:426, 1917.

The German literature for 1919 contains numerous articles on the "Sachs-Georgi reaction."[38] The test is a precipitation in serum by means of cholesterolized organ extracts. The Meinike reaction[39] is based on the same principles with minor differences in the technic. The technic of the Sachs-Georgi reaction is very simple, but the test is time consuming in that it is not read for from twenty-four to forty-eight hours. In the many articles published there appear but few unfavorable comments on the test. It parallels the Wassermann reaction in from 78 to 94 per cent. The clinical comparison is even better.[40] It is the opinion of some[41] that because of its simplicity and reliability it will probably supersede the Wassermann. Sachs and Georgi[42] found the reaction less sensitive than the Wassermann test in the cerebrospinal fluid but it gives a characteristic qualitative reaction. McCann,[43] working with tests formerly proposed and similar in their nature to the Sachs-Georgi reaction, found that the best results were given by the one proposed by Herman and Perutz. Even this was only partially specific. Between 70 and 75 per cent. of Wassermann positive serums gave positive results, and two of eleven Wassermann negative serums gave positive results.

Kolmer and Toyama[44] describe a coagulo reaction which is very delicate and a constant characteristic of syphilis. The technic is very simple but the test is scarcely practicable because of the difficulty of preparing reagents. The test is based on the observation of Hirschfeld and Klinger that syphilitic serum inhibits or delays the formation of thrombin and consequently of coagulation by an inactivating influence on cytozyme, one of the essential elements in thrombin formation. Uemura[45] reports that this test as elaborated by him is in many cases distinctly superior to the Wassermann.

THE COLLOIDAL GOLD TEST

Practically all writers on the subject agree that the colloidal gold test is of great clinical value. It is the most sensitive indicator we have of pathologic changes in the cerebrospinal fluid. If the colloidal gold reaction is negative, it is highly probable that the Wassermann

38. Sachs and Georgi: Med. Klin. **14**:805 (Aug. 18) 1918. Georgi: Biochem. Ztschr. **93**:16, 1919. Gaehtgens: München. med. Wchnschr. **66**:933 (Aug.) 1919. Scheer: München. med. Wchnschr. **66**:902 (Aug. 8) 1919. Perutz: Wien. klin. Wchnschr. **32**:953 (Sept. 25) 1919. Lesser: Berl. klin. Wchnschr. **56**:224 (March 10) 1919.

39. Meinicke: München. med. Wchnschr. **66**:932 (Aug.) 1919.

40. Löns: Deutsch. med. Wchnschr. **45**:579 (May 22) 1919.

41. Galli-Valerio: Cor.-Bl. f. schweiz. Aerzte **49**:1977 (Dec. 25) 1919.

42. Sachs and Georgi: Arbeit. a. d. Inst. f. Exper. Therap. **6**:27, 1919.

43. McCann: J. Lab. & Clin. M. **4**:742 (Sept.) 1919.

44. Kolmer and Toyama: Am. J. Syphilis **2**:505 (July) 1918.

45. Uemura: Am. J. M. Sc. **154**:533 (Oct.) 1917.

reaction is also negative.[46] Weston [47] gives a good review of the test with methods and directions and the characteristics of a good solution. The nature of the substance causing the reaction is discussed. Chemically, the test shows the amount of globulin present and indirectly the amount of albumen. The Wassermann reacting substance and the gold precipitating substance are separable constituents.

SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

There is considerable evidence to show that the nervous system is infected very early in syphilis and it is the general opinion that it is infected only then. As to the frequency of central nervous infection there is no accurate knowledge. Klauder [48] gives a very good review of the situation in regard to acquired syphilis. He cites instances in which the only abnormality is the cerebrospinal fluid early in the disease was the presence of treponema pallida. He thinks it logical to assume that the spirochetes invade the nervous system in every case, and that such invasion may be unaccompanied by laboratory or clinical evidence except the finding of treponemas in the fluid. This assumption is borne out by Warthin,[49] who found in practically every case of latent or clinical syphilis necropsied some degree of thickening of the meninges. The dura was constantly more adherent and thickened, although no active foci were ever found in this membrane. Focal thickening of the leptomeninges were found in practically every case, more frequently in the arachnoid than in the pia. The great majority of these were healed inactive areas. He believes that every case of old syphilis will present some scattered perivascular infiltrations of lymphocytes and plasma cells as are found in all other organs and tissues. These areas represent the local reaction to the presence of spirochetes.

As judged by the examination of the cerebrospinal fluid, a varying proportion of syphilitics show evidence of central nervous involvement depending on the standard set for normal cerebrospinal fluid. Jeans [50] found from a review of the literature that practically one-third of all patients in the early stages of acquired syphilis and an equal number in the later stages showed conspicuous changes in the cerebrospinal fluid, which changes strongly indicated invasion of the central nervous system. He has observed marked changes in the cerebrospinal fluid, including a positive Wassermann reaction, in practically one-third of

46. Vogel: Arch. Int. Med. **22**:496 (Oct.) 1918.
47. Weston: Am. J. Syphilis **3**:266 (April) 1919.
48. Klauder: Am. J. Syphilis **3**:559 (Oct.) 1919.
49. Warthin: Am. J. Syphilis **2**:425 (July) 1918.
50. Jeans: Am. J. Dis. Child. **18**:173 (Sept.) 1919.

214 infants and children with hereditary syphilis. Of those with pathologic cerebrospinal fluids, one-third of the infants and two-thirds of the older children had clinical evidence of nervous involvement. If the assumption is correct that the nervous system is infected in every instance, it is equally logical to assume that spontaneous resolution takes place in about two-thirds of the cases both in acquired and hereditary syphilis. Many writers emphasize the importance of cerebrospinal fluid examination of all syphilitics, especially before they are discharged as cured. Such a routine procedure results in not infrequent surprises.

The pathology and course of hereditary neurosyphilis differs from that of acquired neurosyphilis in but few essentials. Arrest of brain development in any particular is a frequent event in hereditary neurosyphilis,[51] while such an event could not occur in a fully developed adult brain. Meningitis in the pathologic sense is very common in the early stages of hereditary syphilis. Syphilitic involvement of the meninges with definite clinical signs of meningitis is surely not so uncommon as the scattered case reports would lead us to believe. Bly [52] reports one case and cites seven others. Exclusive of these, Hutinel [53] and Snow [54] each report a case. The ages of the patients ranged from 1 to 10 years. Jeans [50] observed seven cases, the ages ranging from 3 months to 4½ years.

There is practically no recent literature on cranial nerve involvement in hereditary syphilis. MacKenzie [55] gives a very good review of the pathology of syphilis of the inner ear and eighth nerve in hereditary and acquired syphilis. In the majority of instances of early hereditary syphilis the meninges are first attacked, the nerve next and eventually the labyrinth. But little is known of the pathology of the later cases. He [56] reports two cases of nerve deafness which completed Hutchinson's triad at the ages of 34 and 44, respectively. Green [57] found optic neuritis or optic atrophy in sixteen of 100 syphilitic infants and children. Klauder [48] states that in acquired syphilis the cranial nerves are involved in the following order of frequency: eighth, second, third, fourth, fifth, sixth and seventh. The involvement is either a neuritis or due to exudate around the nerve. In the majority of instances, in the case of the eighth nerve both the cochlear and vestibular branches are involved bilaterally.

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51. Wohlwill: Dermat. Wchnschr. **67**:843 (Dec. 14) 1918; Arch. f. Psychiat. **59**:733, 1918.
52. Bly: Am. J. Syphilis **2**:712 (Oct.) 1918.
53. Hutinel: Presse méd. **26**:205 (April 22) 1918.
54. Snow: Am. J. Dis. Child. **16**:161 (Sept.) 1918.
55. Mackenzie: Am. J. Syphilis **2**:9 (Jan.) 1918.
56. Mackenzie: Am. J. Syphilis **2**:241 (April) 1918.
57. Green: Tr. Am. Ophth. Soc. **17**:528, 1919.

The eighth nerve has recently received considerable attention. Instances of marked involvement are relatively uncommon, but minor changes are so common in acquired syphilis even in the very early stages that functional tests of hearing have been considered as possible aids in diagnosis not only of neurosyphilis, but of syphilis in general. Jones [58] states that the eighth nerve, because of its extensive ramifications and its apparent greater susceptibility to toxemia, is the most likely part of the nervous system to be affected. Until recently the degree of function has been determined largely by tuning fork tests which show in syphilitic involvement lowered bone conduction and impairment of hearing for high tones. Goeckermann, Barlow and Stokes [59] found the lowered bone conduction test positive in 78 per cent. of known syphilitics, but also positive in 49 per cent. of non-syphilitic patients tested. They conclude that because of the high factor of error, the test has only a restricted value as a diagnostic aid in syphilis. Downey,[60] in 1917, reviewed the situation in the very early stages of syphilis.

According to Jones [58] and MacKenzie,[56] these tuning fork tests have their value, but lack the precision and definiteness of the newer tests which are much more delicate and constitute an objective measurement. The degree of function is expressed with mathematical precision. By these tests devised by Robert Bárány the labyrinth is examined. The semicircular canals are stimulated by revolving the person in a turning chair, by douching the ears with either hot or cold water or by applying a galvanic current to the ears. The phenomena produced are nystagmus and vertigo which vary in their degree, duration and direction from the normal. There are no tests of any other cranial nerves which compare in delicacy and accuracy with these tests of the eighth nerve. According to Jones, these tests are very useful in the diagnosis of syphilis and in watching the progress and result of treatment.

As judged from the published case reports, tabes is quite rare as a result of hereditary syphilis. Southard and Solomon [61] report a case in a patient aged 12 years; Lereboullet and Mouzon [62] one in a patient aged 15 years, and Galliot [63] reports two cases at 29 and 36 years, respectively, developing under the stress of the campaign.

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58. Jones: Equilibrium and Vertigo, Philadelphia, J. B. Lippincott Co., 1918, p. 47.
59. Goeckermann, Barlow and Stokes: Am. J. Syphilis **3**:240 (April) 1919.
60. Downey: Am. J. Syphilis **1**:616 (July) 1917.
61. Southard and Solomon: Neurosyphilis, Boston, W. M. Leonard, 1917.
62. Lereboullet and Mouzon: Paris méd. **9**:20 (Jan. 4) 1919; abstr., J. A. M. A. **72**:613 (Feb. 22) 1919.
63. Galliot: Paris méd. **9**:462 (June 7) 1919; abstr., J. A. M. A. **73**:371 (Aug. 2) 1919.

Paresis, though uncommon in hereditary syphilis, is somewhat more frequent than tabes. Ash [64] reports three cases in patients aged 6, 10 and 14 years, respectively. Ricksher [65] reports three cases with the pathologic findings. Southard and Solomon [61] report seven cases and quote previously recorded cases.

On the whole, the result of treatment of paresis in adults has been disappointing. Long remissions have occurred as a result of treatment, and in a few there has been complete arrest as long as followed. Others have had uniformly bad results. Even less has been accomplished with true paresis in childhood. The course is shorter and remissions are rare. The pathology in the child is the same as in the adult.

Valente [66] cites numerous modern authors who do not believe that paresis is due to the direct action of the spirochete, the belief being based, in part, on the fact that spirochetes are not often found in the brain. He cites other observers as having found them in the brains of paretics as follows: Gerber, Benedict and Tater, 4.5 per cent. of twenty-two cases; Marinesco and Minea, 7 per cent. of twenty-seven cases; Noguchi, 24 per cent. of 200 cases; Levaditi, Marie and Bankowski, 27 per cent. of forty-eight cases, and Foster and Tomaczewski 44 per cent. of sixty-one cases. Valente, himself, found spirochetes in 70 per cent. of forty cases, and feels certain that if his search had been continued he would have found them in 100 per cent. Because part of the study was made on living patients, he was often unable to make a sufficiently extensive search. In some of the necropsy material he found enormous numbers in the cortex, more than are commonly seen in the organs in hereditary syphilis.

That some change has occurred in the spirochetes found in paretic brains seems established. Wile and DeKruif [67] found numerous short, thick forms and but few spirals when paretic brain material was inoculated into rabbit testis. They found that cultures grew much more slowly and much less luxuriantly than do those cultivated from early cutaneous and mucous membrane syphilis. Valente [66] inoculated sixty-seven rabbits with paretic brain cortex. None was successful and testicular puncture showed no spirochetes, nor did microscopic examination of the testes show any syphilitic lesions. This was not due to faulty technic, because he was successful with other material. He cites the work of others who were similarly unsuccessful and concludes that in paresis the treponemas must have undergone considerable diminution in virulence for rabbits.

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64. Ash: Arch. Pediat. **35**:156 (March) 1918.
65. Ricksher: Alienist & Neurol. **39**:8 (Jan.) 1918.
66. Valente: Arquivos d. Inst. Bacteriol. **5**:29, 1918.
67. Wile and DeKruif: J. A. M. A. **66**:646 (Feb. 26) 1916.

That syphilis is a cause of mental deficiency there can be no doubt,[68] though the extent to which it is a cause is in dispute. Kuhlmann[69] found that the frequency of syphilis in the general population runs nearly as high as in the feebleminded. Higgins,[70] on the other hand, found 42 per cent. of fifty mentally defective children to have positive Wassermann reactions, and he quotes the frequency found by other authors as follows: Gordon, 50 per cent. of seventy-five; Fraser, 45 per cent. of ninety-nine; Watson, 60 per cent. of 204. Jeans[50] found that of twenty-five children having clinical evidence of neurosyphilis, twelve had gross mental defect associated.

Hutinel and Nadal[71] observed that acute infections may serve to light up a quiescent hereditary neurosyphilis. They cite a case of syphilitic hemiplegia occurring during measles in a child, aged 4 years. Menninger[72] has noted the same effect in the case of influenza and acquired neurosyphilis.

SYPHILIS OF THE EYES

Green[57] reviewed the literature on the eye in hereditary syphilis and reported his own findings in 100 cases. The incidence of eye lesions in hereditary syphilis has been given by Rabl as 39 per cent. in 127 cases, and by Fournier as 48 per cent. in 212 cases, presumably including all ages of children. Igersheimer found pathology in 80 per cent. of twenty-seven nurslings. Lesions of the lids, conjunctiva, lacrimal apparatus and lens are either rare or secondary to other lesions and are relatively unimportant. Of 2,000 collected cases of hereditary syphilis, keratitis occurred in 50 per cent. A frequent association of retinochoroiditis with keratitis has been observed, usually occurring after the keratitis. A vertically oval cornea has been claimed to be more frequent in hereditary syphilis and to be a precursor of keratitis. Iritis is infrequent as compared to acquired syphilis. Its incidence is really unknown because it is not routinely looked for. A vitreous haze in childhood means hereditary syphilis. It is often associated with retinochoroiditis. Optic neuritis was found by Heine in 82 per cent. of 105 babies. Most of these must have been physiologic variations. Other observers have failed to find such a large number.

In his own study of 100 syphilitic infants and children, Green reports findings as follows: 74 showed abnormality; 9 had fixed or unequal pupils; 4 had strabismus; 1 had ptosis; 3 had nystagmus; 19

68. Gaines: Am. J. Syphilis **2**:474 (July) 1918.
69. Kuhlmann: Journal-Lancet **38**:215 (April 15) 1918.
70. Higgins: Am. J. M. Sc. **155**:549 (April) 1918.
71. Hutinel and Nadal: Paris méd. **9**:442 (Dec. 6) 1919; abstr., J. A. M. A. **74**:286 (Jan. 24) 1920.
72. Menninger: Arch. Int. Med. **24**:98 (July) 1919.

had had keratitis or evidence of past keratitis; 2 had fine haze in the vitreous; 52 had pathologic changes in the eye grounds. There was hardly a single pathologic eye ground that did not present lesions of diverse types, i. e., mixed varieties of involvement predominated. Of those with pathologic eye grounds, eight had optic neuritis; eight had optic atrophy, and twenty-eight had peripheral and central punctate pigmentation. This pigmentation consisted of tiny dots of brown or brown black pigment strewn fairly evenly over the retina. Between the dots are minute yellowish red spots. Three had peripheral punctate depigmentation; 5 showed large irregular areas of retinochoroidal atrophy; 4 had masses of gray pigment alternating with depigmented areas; 2 had disseminated retinochoroiditis; 1 had neuroretinitis punctata; 2 had retinal hemorrhages; 3 had perivascularitis. Green is convinced that the dark brown punctate pigmentation he describes is characteristic of hereditary syphilis. He found this appearance in but two adults, and one of these had scars of old keratitis.

SYPHILIS OF THE EARS

This subject is dealt with at some length under the nervous system. Fraser and Muir [73] describe the pathology of hereditary syphilitic disease of the ear. In young children there exists at present very indefinite knowledge of the changes which occur. From clinical observation it would seem that otitis is very common in syphilitic children. The middle ear symptoms are soon replaced by those of the inner ear. The catarrhal affections developing into a condition clinically corresponding to otosclerosis. The original otitis may possibly be syphilitic, or if pyogenic may progress because of lowered resistance. The microscopic examination in a case of late syphilis is reported in detail.

SYPHILIS OF THE NOSE

No recent observations on the nose in hereditary syphilis have been found. Beck [74] states that the secondary stage of acquired syphilis manifests itself in the nose as an exanthem of macular or papular type. Within the nose these reddish spots frequently become confluent and appear like any other form of coryza. The only way one may differentiate it from simple acute coryza, aside from the presence of spirochetes and the Wassermann reaction, is that the secretion is not marked and the disease is more protracted. Graham [75] describes a peculiar bluish appearance of the nasal mucous membrane in chronic syphilis; also a peculiar sinus involvement and middle ear disease.

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73. Fraser and Muir: J. Laryngol., Rhinol. & Otol. **32**:8 (Jan.) 1917.
74. Beck: New York State J. M. **17**:290 (June) 1917.
75. Graham: Am. J. Syphilis **3**:26 (Jan.) 1919.

TEETH

To properly evaluate changes in the teeth from the normal as a diagnostic aid in hereditary syphilis, it is necessary to know much of the embryology of tooth formation. Such information in relation to syphilis is admirably stated by Stein.[76] The effect of syphilis on the teeth is one of disturbed nutrition which affects the enamel or dentine, or both, of that part of the tooth which is being laid down at the time of the disturbance. According to the literature, such changes are practically never seen in the first teeth, probably for the reason that these teeth have their beginning between the seventeenth and eighteenth week of intrauterine life, and the occurrence of syphilis at that early date in so severe a form as to affect the teeth results in the death of the fetus. In the permanent teeth occur the changes which are commonly known to be associated with hereditary syphilis. These are described in detail by Stein. Syphilis may cause the complete arrest of development of the dentinal germ or follicle, thus resulting in the absence of certain teeth. The absence of certain permanent teeth may result in the persistence of corresponding teeth of the first set, an event which Stein states is more frequent than is generally supposed or recognized. Such persistence of the deciduous teeth is a very important diagnostic sign. It occurs, according to Stein, in the following order of frequency: Second molars, first molars, cuspids, incisors. Not infrequently a fifth cusp is found on the first molar teeth. LaCapere and Laurent[6] find that the presence of this extra cusp has no connection with syphilis.

ALIMENTARY TRACT

Gaucher[77] states that fissuring of the tongue, such as he describes in detail, is a certain indication of acquired or hereditary syphilis.

Tanturri[78] describes a palate sign in hereditary syphilis. The edge of the soft palate as it arches to the uvula has a characteristically irregular outline. It looks dentated, lacelike, instead of a smooth edge, as if eroded. There may be a loss of substance for from 1 to 2 mm. from the edge. The flexibility and color of the palate are not modified. He has observed this sign at all ages, from birth to 20 years, and thinks that it should be accepted as positive testimony of hereditary syphilis.

DeRezende[79] describes an enterocolitis occurring in the new-born as the result of syphilis. The condition usually appears immediately

76. Stein: Med. Rec. **90**:445 (Sept. 9) 1916.
77. Gaucher: Ann. d. mal. ven., June, 1917; abstr., Am. J. Syphilis **3**:149 (Jan.) 1919.
78. Tanturri: Pediatria **27**:4 (Jan.) 1919.
79. DeRezende: Brazil Medico **33**:297 (Sept. 20) 1919; abstr., J. A. M. A. **73**:1861 (Dec. 13) 1919.

after birth, is characterized by tenesmus and by frequent stools of greenish mucus with or without blood. The infant often screams with pain. Specific treatment without dietary change restores health.

Bauer [80] reports a case of syphilis of the liver with its onset at the age of 11 months. The liver became greatly enlarged, fever was present and jaundice and ascites appeared. Necropsy showed a diffuse hepatitis with intralobular sclerotic atrophy of the parenchyma.

Pentagna [81] reports a case of syphilitic cirrhosis of the liver which began at the age of 24 months. The child had the ascitic fluid withdrawn thirty-one times and died at the age of 34 months. The necropsy showed a Laennec cirrhosis in the hyperplastic stage.

Castex and co-workers [82] have written rather extensively on the gastro-intestinal diseases that occur in adult life as a result of hereditary syphilis. They have observed various bands and kinks, gastroduodenal ulcer and perivisceritis or chronic peritonitis due to inherited infection.

SYPHILIS OF THE LUNGS

Canelli [83] recently gave a fairly complete review of hereditary syphilis of the lungs. According to his statement the condition is frequent and difficult of diagnosis. Often the diagnosis is made only anatomically. The principal forms are gumma, bronchiectasis and pneumonia. The bronchiectasis is primary in some cases. The pneumonias are interstitial, epithelial (desquamative), fibrosclerotic and adenomatous. There may be association of these diverse forms. The pleura rarely is involved. Pulmonary syphilis exists in association with other pulmonary processes, particularly tuberculosis. The histologic changes are complex and multiple. Spirochetes are most frequently found in pneumonia alba.

Plique [84] asserts that the lungs are affected in syphilis with nearly the same frequency as are the bones. It is his opinion that tracheobronchial adenopathy in syphilitic children is generally of syphilitic origin. The late stage of the disease usually appears in the lungs about the fifth year, though it may not appear until adolescence.

Leredde [85] describes twenty cases of acute bronchitis with pulmonary congestion, some presenting emphysema and asthma. The

80. Bauer: Arch. Pediat. **34**:927 (Dec.) 1917.
81. Pentagna: Pediatria **25**:140 (March) 1917.
82. Castex and Delfor: Prensa méd. Argentina **6**:57 (July 30) 1919; abstr., J. A. M. A. **73**:1810 (Dec. 6) 1919. Castex and Rosso: Prensa méd. Argentina **6**:25 (June 20) 1919; abstr., J. A. M. A. **73**:1169 (Oct. 11) 1919.
83. Canelli: Pediatria **27**:11 (Jan.) 1919.
84. Plique: J. de méd. et de Chir. Pratiques **89**:321, 1918; abstr., Am. J. Syphilis **3**:467 (July) 1919.
85. Leredde: Ann. d. mal. ven. **13**:760, 1918; abstr., Am. J. Syphilis **3**:468 (July) 1919.

lung process was one of syphilitic sclerosis of an active character, a condition which predisposes to other lung diseases. Antisyphilitic treatment may give results not anticipated from the clinical picture.

GENITO-URINARY

Hutinel,[86] writing on nephritis in hereditary syphilis, describes an acute type in two children, aged 19 months and 4 years, respectively, and a chronic type in two children, aged 11 and 13 years, respectively. The nephritis does not assume a special type. The condition is not so much a nephritis as that renal reactions are modified by the specific infection. Uremic manifestations are rare and tardy. He thinks that mercury is not advisable in the treatment of nephritis of syphilis and has witnessed hematuria following its use. He uses arsphenamin intravenously. Rapid improvement or definite cure can be counted on only in the early stage. Because the lesion is restricted to circumscribed regions there is better hope of cure than with ordinary nephritis.

Lange [7] states, from necropsy observation on infants, that kidney syphilis is underestimated because of the small amount of clinical evidence. The changes found were mostly interstitial and delayed development. In prematures and still-births, interstitial changes predominated; in infants, parenchymatous changes (atrophy, cloudy swelling and fatty degeneration). Of his cases, 11 per cent. showed urine changes. Of these, five were specific and six were doubtful. In five cases blood was prominent in the urine. Mercury made none of the patients worse. He states that specific hemorrhagic nephritis was seen three times by Hahn.

Levy and Guilé [87] found spirochetes in the urine of only one of twenty-four men examined near the beginning of the secondary stage. Zimmerman and Levy [88] discovered no striking bladder change on cystoscopic examination of twenty-four patients with acquired syphilis in the secondary stage.

BONES AND JOINTS

Post [89] gives an excellent summary of the bone lesions of hereditary syphilis. However, no new knowledge is presented. Roberts [90] describes a series of cases of hereditary syphilis observed in an orthopedic clinic. In this group there were 81 joint conditions simulating

86. Hutinel: Paris méd. **9**:65 (Jan. 25) 1919; abstr., J. A. M. A. **72**:902 (March 22) 1919.
87. Levy and Guilé: Bull. et mém. Soc. méd. d. hôp. **43**:48 (Jan. 24) 1919; abstr., J. A. M. A. **72**:1332 (May 3) 1918.
88. Zimmermann and Levy: J. Urol. **3**:407 (Oct.) 1919.
89. Post: J. Cutan. Dis. **34**:351 (May) 1916.
90. Roberts: Am. J. Syphilis **3**:587 (Oct.) 1919.

tuberculosis; 17 cases of myositis, some of which presented symptoms usually attributed to sacroiliac strain, 24 cases of arthritis; 8 of disease of the tarsus or carpus; 16 of chronic headaches; 10 cases of osteochondritis of the hip; 1 case of lateral curvature; 33 cases of caries of the spine and 1 case of lymphangitis. Of the total of 226 patients, a Wassermann test was made in forty-seven. The reaction was weakly positive or negative in all. These patients improved with mercury and potassium iodid so remarkably that he argues that either syphilis was a factor in the production of these disorders or else in mercury and potassium iodid we have two remedies whose efficacy has not been fully appreciated.

SKIN

Hirschler [91] reported the case of a colored patient, 5 weeks of age, who ten days previously developed vesicular syphilides of the face, hands and feet. The eruption looked like little pearls. He states that a vesicular eruption is one of the rarest of syphilitic manifestations.

Papers on the relation of vitiligo and syphilis are found with considerable frequency in the recent literature. Lane [92] summarized the published knowledge of this relationship. His collected statistics show that from 40 to 50 per cent. of persons with vitiligo, who have been studied in this respect, have been said to have syphilis. He states that it is impossible to arrive at the definite conclusion that there is a relation of cause and effect between syphilis and vitiligo, but the intensive study of the cases is causing this hypothesis to gain ground. Up to the present, no other disease has been demonstrated to be present in anything like this proportion in patients with vitiligo. Ravitch and Steinberg [93] also believe that at present our knowledge is insufficient for definite conclusions. They think that syphilis may be the cause in some cases, but not in all cases of vitiligo.

MISCELLANEOUS OBSERVATIONS

Adair [94] proved syphilis to be present in two of five cases of hemorrhagic disease of the new-born.

Lütjohann [95] reports a case of Raynaud's disease in a 5-year-old girl with auto-amputation of both legs and finally death. He cites eight other cases in the literature, and thinks that the entire disease may be traced to syphilitic changes in the vessel walls.

Costex and Palacio [96] think that hereditary syphilis has a con-

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91. Hirschler: J. Cutan Dis. **35**:105 (Feb.) 1917.
92. Lane: J. A. M. A. **73**:27 (July 5) 1919.
93. Ravitch and Steinberg. Am. J. Syphilis **2**:479 (July) 1918.
94. Adair: Am. J. Obst. **78**:678, 1918.
95. Lütjohann: Monatschr. f. Kinderh. **15**:58, 1918.
96. Castex and Palacio: Prensa méd. Argentina **6**:105 (Sept. 20) 1919; abstr., J. A. M. A. **73**:1968 (Dec. 27) 1919.

siderable share in the pathogenesis of Banti's disease, aleukemic lymphadenosis in children, paroxysmal hemoglobinuria, chronic hemolytic jaundice with enlarged spleen and glandular disease in the neck in adults.

In the syphilitic babies studied by Lange [7] anemia was present in 18 per cent. A decrease in both the hemoglobin percentage and the number of red blood cells was present. No specific blood picture was noted. Both erythroblasts and myelocytes were noted, though the myelocytes were observed only in patients with osteochondritis.

From forty-three necropsies on syphilitic infants, Lange concludes that when the disease is clinically limited to the skin most of the organs were free of syphilis whether the patient was treated or not. He concludes that infants with skin syphilis have a better prognosis than those with visceral syphilis.

Contagion of hereditary syphilis is rare in infants as compared to other infectious diseases of childhood.[97] Werther [98] records ten instances in which nurses had been infected by infants. Steinert [99] records three instances in which wet nurses had been infected, and four instances in which the caretaker had been infected. In the case of the wet nurses the primary sore appeared on the breast, and in the caretakers it appeared in the throat.

A new diagnostic sign for hereditary syphilis has been described by Abrams.[100] The subject faces the west with the feet on a grounded plate and with the hand elevated in proximity to a window. After 30 seconds a circumscribed pallor is demonstrable at the terminal phalanges of all the fingers, notably the little finger, at definite points at the palmar surface of the terminal phalanges and on the inner surface and extreme end.

Valente [101] successfully inoculated rabbit testis with the blood from syphilitics in the primary stage in two cases, and in the secondary stage in three of four cases studied. Neither he nor Uhlenhuth were able to observe spirochetes in the blood which was infectious for rabbits. Uhlenhuth and Mulzer [102] found that blood from cases of early syphilis infected rabbits, but they were unsuccessful in the case of latent and tertiary syphilis. These observations have a bearing on the mechanism of recurrence of syphilitic lesions and on maternal transmission. A view which formerly was held in greater favor than

97. Pfaundler: München. med Wchnschr. **65**:161 (Feb. 5) 1918.
98. Werther: München. med. Wchnschr. **65**:71 (Jan. 15) 1918.
99. Steinert: Jahrb. f. Kinderh. **40**:27, 1919.
100. Abrams: Med. Rec. **94**:103, 1918; abstr., Am. J. Syphilis **2**:803 (Oct.) 1918.
101. Valente: Arquivos d. Inst. Bacteriol., Camera Pestana **5**:1, 1918.
102. Uhlenhuth and Mulzer: Berl. klin. Wchnschr. **54**:645 (July 2) 1917.

now is that from time to time the blood stream becomes infected from old foci, and that gummatous or other changes result in the areas in which the treponemata are newly deposited. The view more in favor is that a septicemia exists only a single time and that late lesions are due to early implantation and a later lighting up in loco.[9]

Warthin [103] presents a new method by which spirochetes may be stained rapidly in tissue sections. Only three days are required, and the results are more certain than with the Levaditi method. Another advantage is that the same paraffin block can be used as for other histologic examination. The stain may be finished twelve hours after the histologic examination of preceding sections shows the desirability of such a stain.

Noguchi [13] discusses the question of immunity of syphilis in considerable detail. Vaccination with dead or avirulent organisms gives no effective immunization. Agglutinins have been demonstrated in rabbits.

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103. Warthin and Starry: Am. J. Syphilis **4**:97 (Jan.) 1920.